IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EDWARDS LIFESCIENCES AG and EDWARDS LIFESCIENCES LLC, Plaintiffs, v. COREVALVE, INC. Defendant.	Case No. 08-091-GMS

DECLARATION OF MICHAEL BECK

MICHAEL BECK, pursuant to 28 U.S.C. § 1746, declares as follows:

1. I am associated with the law firm Paul, Weiss, Rifkind, Wharton & Garrison LLP ("Paul Weiss"), counsel for Plaintiffs Edwards Lifesciences AG and Edwards Lifesciences LLC in the above-captioned matter. I submit this Declaration in support of Plaintiffs' Opposition to Defendant CoreValve, Inc.'s Motion to Transfer Venue to the Central District of California.

2. Attached as Exhibit 1 is a true and correct copy of an Edwards Lifesciences December 15, 2003 press release entitled *Edwards Lifesciences to Acquire Percutaneous Valve Technologies, Inc. for $125 Million*, available on the Edwards Lifesciences website at http://www.edwards.com/newsroom/nr20031215.htm.

3. Attached as Exhibit 2 is a true and correct copy of an Edwards Lifesciences January 27, 2004 press release entitled *Edwards Lifesciences Completes Acquisition of Percutaneous Valve Technologies for $125 Million*, available on the Edwards Lifesciences website at http://www.edwards.com/newsroom/nr20040127.htm.

4. Attached as Exhibit 3 are true and correct copies of biographical information for the inventors of the patents in suit—Dr. Henning Rud Andersen, Dr. John Michael Hasenkam, and Dr. Lars Lyhne Knudsen—available on the Aarhus University website at http://www.au.dk/.

5. Attached as Exhibit 4 is a true and correct copy of H. R. Andersen, L. L. Knudsen, and J. M. Hasenkam, *Transluminal Implantation of Artificial Heart Valves*, 13 European Heart J. 704 (1992).

6. Attached as Exhibit 5 is a true and correct copy of L. L. Knudsen, H. R. Andersen, and J. M. Hasenkam, *Catheter-Implanted Prosthetic Heart Valves*, 16 Int'l J. of Artificial Organs 253 (1993).

7. Attached as Exhibit 6 is a true and correct copy of *CoreValve Could Go Public in 2007, Readies Next-Gen Catheter for Europe*, 31 "The Gray Sheet" 17 (Nov. 21, 2005), *available at* http://www.thegraysheet.com/.

8. Attached as Exhibit 7 is a true and correct copy of an interview with Dr. Jacques R. Seguin published as *Feature: Percutaneous Aortic Valve Replacement with a Self-Expanding Stent: The CoreValve ReValving™ Procedure*, 12 Cath Lab Digest 26 (Nov. 2004), *available at* http://www.cathlabdigest.com/article/3276.

9. Attached as Exhibit 8 is a true and correct copy of Eberhard Grube, MD et al., *Percutaneous Aortic Valve Replacement for Severe Aortic Stenosis in High-Risk Patients Using the Second- and Current Third-Generation Self-Expanding CoreValve Prosthesis*, 50 J. of the Am. Coll. of Cardiology 69 (July 3, 2007).

10. Attached as Exhibit 9 is a true and correct copy of Vita Reed, *Investors Back Pair of Heart Device Makers*, Orange County Business Online, Apr. 2, 2007,

http://ocbj.com/archive_article.asp?aID=12531638.90834102.1454921.8695155.9711464.414&aID2=111908.

11. Attached as Exhibit 10 is a true and correct copy of a CoreValve May 16, 2007 press release entitled *CoreValve Receives CE Mark Approval for its ReValving™ System and Announces Plans to Initiate Expanded Clinical Evaluation*, available on the CoreValve website at http://www.corevalve.com/Press/43.pdf.

12. Attached as Exhibit 11 are true and correct copies of selected pages from the file histories of the three Andersen et al. United States patents in suit—U.S. Patent Nos. 5,411,552; 6,168,614; and 6,582,462 (collectively, "Andersen Patents"). These pages identify seven patent attorneys who appeared of record in the prosecution of the Andersen Patents before the United States Patent and Trademark Office ("USPTO")—Richard H. Tushin, James M. Heslin, Jens E. Hoekendijk, Mark D. Barrish, E. Richard Skula, Brian S. Tomko, and Thomas Spinelli.

13. Attached as Exhibit 12 is a true and correct copy of an April 7, 2008 search of the USPTO patent-attorney online database, which indicates the current location of the foregoing patent attorneys:

Richard H. Tushin (Washington, DC)

James M. Heslin (Palo Alto, California)

Jens E. Hoekendijk (San Francisco, California)

Mark D. Barrish (Palo Alto, California)

Emil Richard Skula (New Brunswick, New Jersey)

Brian S. Tomko (New Brunswick, New Jersey)

Thomas Spinelli (Garden City, New York)

14. Attached as Exhibit 13 is a true and correct copy of excerpts from Johnson & Johnson's 2007 Annual Report.

15. Attached as Exhibit 14 are true and correct copies of an Edwards Lifesciences May 10, 2007 press release entitled *Edwards Lifesciences Initiates Patent Infringement Litigation Against CoreValve*, available on the Edwards Lifesciences website at http://www.edwards.com/newsroom/nr20070510.htm, and an Edwards Lifesciences February 12, 2008 press release entitled *Edwards Lifesciences Initiates Patent Infringement Litigation Against CoreValve in the U.S.*, available on the Edwards Lifesciences website at http://www.edwards.com/newsroom/nr20080212.htm.

16. Attached as Exhibit 15 is a true and correct copy of relevant portions of a transcript from the Edwards Lifesciences Third Quarter (2007) Earnings Call, available at http://seekingalpha.com/article/50887-edwards-lifesciences-corp-q3-2007-earnings-call-transcript.

17. Attached as Exhibit 16 is a true and correct copy of Percutaneous Valve Technologies Inc.'s Certificate of Incorporation filed July 21, 1999, with the Secretary of State of Delaware.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on April 21, 2008.

MICHAEL BECK

CERTIFICATE OF SERVICE

I hereby certify that on April 21, 2008 I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing to:.

Frederick L. Cottrell, III, Esquire
Chad M. Shandler, Esquire
RICHARDS, LAYTON & FINGER, P.A.

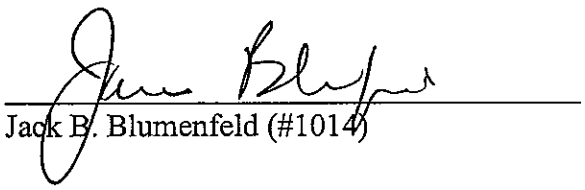
I further certify that I caused to be served copies of the foregoing document on April 21, 2008 upon the following in the manner indicated:

Frederick L. Cottrell, III, Esquire
Chad M. Shandler, Esquire
RICHARDS, LAYTON & FINGER, P.A.
One Rodney Square
920 North King Street
Wilmington, DE 19801

VIA ELECTRONIC MAIL and HAND DELIVERY

J. David Evered, Esquire
Joseph R. Re, Esquire
Joseph S. Cianfrani, Esquire
KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 Main Street
Fourteenth Floor
Irvine, CA 92614

VIA ELECTRONIC MAIL



Jack B. Blumenfeld (#1014)

EXHIBIT 1

Edwards Lifesciences to Acquire Percutaneous Valve Technologies, Inc. for $125 Million

• New Technology Expands Market With Interventional Alternative for Patients With Heart Valve Disease

IRVINE, Calif., Dec. 15-- Edwards Lifesciences Corporation (NYSE: EW), a global leader in medical technologies to treat advanced cardiovascular disease, and the world's number-one heart valve company, announced today that it has entered into a definitive agreement to acquire Percutaneous Valve Technologies, Inc. (PVT), a privately held medical technology company based in Fort Lee, NJ with a subsidiary in Caesarea, Israel, and a leader in the development of an innovative, catheter-based (percutaneous) approach for replacing aortic heart valves. Under terms of the agreement, Edwards would pay $125 million in cash upon completion of the transaction, plus up to an additional $30 million in payments upon the achievement of key milestones. The transaction is expected to close in the first quarter of 2004, subject to customary closing conditions. Edwards has the right to terminate the agreement for a payment of up to $15 million.

"This transaction will allow Edwards to accelerate the development of a breakthrough technology for patients with heart valve disease, particularly the many individuals who do not receive surgery today," said Michael A. Mussallem, Edwards' chairman and CEO, who noted that sales of catheter-based valve repair and replacement products could exceed $1 billion over the next decade.

"Edwards has been developing its own unique percutaneous heart valve therapy platform, and this transaction enables the company to provide percutaneous technology to clinicians much sooner," Mussallem said. "Although the safety and efficacy of these technologies is not yet established, we believe this transaction should provide a path to leadership in minimally invasive alternatives for patients with heart valve disease. We are very excited about combining Edwards' decades of experience in successfully pioneering the treatment of heart valve disease, with PVT's unique capabilities, clinical experience and strong intellectual property."

Edwards expects to take an initial in-process research and development (IPR&D) charge related to this transaction in the first quarter of 2004, estimated between $60 million and $90 million ($1.00 to $1.50 per share). Excluding this charge, the company believes that the range of dilution related to additional costs will be between $0.10 to $0.15 per share on the current 2004 First Call mean earnings per share estimate of $1.77.

"This decision to marry the capabilities of PVT and its technologies with the breadth and depth of Edwards' global heart valve therapy experience provides the needed expertise and resources to assure successful commercialization. We are eager to become part of the Edwards organization so that we can focus our combined expertise on meeting the needs of thousands of patients worldwide," said Stanton Rowe, PVT president and CEO.

PVT's technology is a proprietary combination of balloon-expandable stent technology integrated with a percutaneously delivered tissue heart valve. Unlike conventional open-heart valve replacement surgery, this less-invasive procedure is designed to be performed in a cardiac catheterization laboratory under local anesthesia.

The first human implant of PVT's valve was performed in April 2002 by Dr. Alain Cribier, who has treated 14 patients to date and is conducting a prospective clinical trial in France. U.S. clinical trials are pending approval of an IDE filing expected early next year. PVT also plans to file for a Humanitarian Device Exemption (HDE) with the U.S. Food and Drug Administration in 2005, which would allow for commercial use in a limited number of patients. CE Mark also is anticipated in Europe in 2005.

"This technology continues to be very promising for patients, particularly those who are not candidates for conventional heart valve surgery today," said Martin Leon, MD, president and CEO of the Cardiovascular Research Foundation in New York, and a PVT co-founder. "When fully developed, this therapy could revolutionize heart valve replacement procedures. Patients could avoid the invasiveness of open-heart surgery, and the recovery period would be dramatically shortened."

"The acquisition of PVT represents an important complement to Edwards' existing heart valve pipeline," added Mussallem, who noted that Edwards is also actively pursuing three of its own percutaneous heart valve development programs, including two approaches for mitral valve repair, and a unique approach for aortic valve replacement.

Endovascular Devices Intended for a New and Growing Population

Each year, an estimated 300,000 people worldwide undergo heart valve replacement or repair surgery. Edwards expects the number of surgical heart valve procedures to continue growing, due in part to the overall increasing incidence of cardiovascular disease, compounded by an aging global population.

Current surgical treatments of heart valve disease offer excellent long- term outcomes as biological valve technology and surgical techniques have improved. However, there is a population of patients who are not being treated today. The goal of percutaneous heart valve therapies is to provide catheter-based alternatives to patients who are not candidates for heart valve surgery.

"We believe that more than one million patients worldwide suffer from symptomatic aortic heart valve disease," Mussallem said. "Only a small portion of patients undergo surgery today, and the promise of percutaneous procedures would be to provide new treatment options for the large number of patients whose heart valve disease remains largely unaddressed."

About PVT

PVT, located in Fort Lee, NJ, with a subsidiary in Israel, is a privately held medical technology company developing an innovative, percutaneous approach for delivering heart valves to treat late-stage aortic stenosis. PVT was founded by Stanton Rowe and Stanley Rabinovich, the company's executive vice president and chief operating officer, along with Martin Leon, MD, president and chief executive officer of the Cardiovascular Research Foundation in New York, and Alain Cribier, MD, chief of Cardiology of University Hospital in Rouen, France.

About Edwards Lifesciences

Edwards Lifesciences, a leader in advanced cardiovascular disease treatments, is the number-one heart valve company in the world, and the global leader in acute hemodynamic monitoring. Headquartered in Irvine, Calif., Edwards focuses on four main cardiovascular disease states: heart valve disease, coronary artery disease, peripheral vascular disease and congestive heart failure. The company's global brands, which are sold in approximately 100 countries, include Carpentier-Edwards, Cosgrove-Edwards, Swan-Ganz, and Fogarty. Additional company information can be found at www.edwards.com.

Conference Call and Web Cast Information

Edwards Lifesciences will be hosting a conference call today at 9:00 a.m. EDT to discuss this transaction. To participate in the conference call, dial (877) 407-8037 or (201) 689-8037. The call will also be available via live or archived Web cast on the "Investor Information" section of the Edwards' Web site at http://www.edwards.com or http://www.edwards.com/conferencecalls. A telephonic replay can be accessed for 72 hours by dialing (877) 660-6853 or (201) 612-7415 and using account number 2995 and passcode 85388.

This news release includes forward-looking statements that involve risks and uncertainties, including those related to the success of animal and clinical studies of percutaneous heart valve replacement, the potential size of the catheter-based heart valve repair and replacement market, the potential for Edwards to provide these technologies to non-surgical candidates even sooner, the ability of this transaction to further strengthen the company's global leadership, and, more generally, the ability to consummate targeted technology investments and acquisitions; timing or results of pending or future clinical trials, actions by the U.S. Food and Drug Administration and European Union technological advances in the medical field, product demand and market acceptance, the effect of changing economic conditions, the impact of foreign exchange, and other risks detailed in the company's filings with the Securities and Exchange Commission. These forward-looking statements are based on estimates and assumptions made by management of the company and are believed to be reasonable, though are inherently uncertain and difficult to predict. Actual results or experience could differ materially from the forward-looking statements.

Contact Information:
Media, Barry R. Liden, +1-949-250-5070, or Investors, David K. Erickson, +1-949-250-6826, both of Edwards Lifesciences Corporation

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EXHIBIT 2

Edwards Lifesciences Completes Acquisition of Percutaneous Valve Technologies for $125 Million

IRVINE, Calif., Jan. 27 -- Edwards Lifesciences Corporation (NYSE: EW), a global leader in medical technologies to treat advanced cardiovascular disease, and the world's number-one heart valve company, announced today that it has completed its acquisition of Percutaneous Valve Technologies, Inc. (PVT), a privately held medical technology company based in Fort Lee, NJ with a subsidiary in Caesarea, Israel. Edwards had announced its intent to acquire PVT in December of 2003.

Under terms of the agreement Edwards is paying the shareholders of PVT $125 million cash, plus up to an additional $30 million in payments upon the achievement of key milestones. Consistent with earlier disclosures, the company expects to take an initial in-process research and development charge related to this transaction in the first quarter of 2004, estimated to be between $60 million and $90 million ($1.00 to $1.50 per share).

The acquisition of PVT reinforces Edwards Lifesciences' leadership role in replacement and repair of heart valves through catheter-based technologies. PVT's technology is an innovative, catheter-based (percutaneous) approach for replacing aortic heart valves, a proprietary combination of a percutaneously delivered balloon-expandable stent technology integrated with a tissue heart valve. Unlike conventional open-heart valve replacement surgery, this less invasive procedure can be performed under local anesthesia, and is a breakthrough for patients who are not candidates for surgery today. Edwards estimates that total sales of catheter-based valve repair and replacement products could exceed $1 billion over the next decade.

""We are pleased at how smoothly this transaction has been completed, and we're looking forward to bringing this technology to market quickly,"" said Michael A. Mussallem, Edwards' Chairman and CEO. ""Our due-diligence on PVT's products, people and intellectual capital has reinforced our enthusiasm about the promise that this technology holds for patients.""

PVT was founded by Stanton Rowe and Stanley Rabinovich, the company's CEO and COO, respectively, along with Martin Leon, MD, president and chief executive officer of the Cardiovascular Research Foundation in New York, and Alain Cribier, MD, chief of Cardiology of University Hospital in Rouen, France.

""We are excited about Stan Rowe and his entire team joining us at Edwards,"" continued Mussallem. ""Stan's leadership abilities, and the depth of experience among the people at PVT, will be important additions to our team.""

The first human implant of PVT's valve was performed in April 2002 by Dr. Alain Cribier, who has treated 17 patients to date and is conducting a prospective clinical trial in France. Edwards plans to file for a Humanitarian Device Exemption (HDE) with the FDA in 2005, which would allow for commercial use in a limited number of patients. CE Mark also is anticipated in Europe in 2005.

Percutaneous Devices Intended for a New and Growing Population

Each year, an estimated 300,000 people worldwide undergo heart valve replacement or repair surgery. Edwards expects the number of surgical heart valve procedures to continue growing, due in part to the overall increasing incidence of cardiovascular disease, compounded by an aging global population.

Current surgical treatments of heart valve disease offer excellent long-term outcomes as biological valve technology and surgical techniques have improved. Percutaneous heart valve therapies could be especially promising for those patients who are not being treated today because they are not candidates for surgery.

About Edwards Lifesciences

Edwards Lifesciences, a leader in advanced cardiovascular disease treatments, is the number-one heart valve company in the world, and the global leader in acute hemodynamic monitoring. Headquartered in Irvine, Calif., Edwards focuses on four main cardiovascular disease states: heart valve disease, coronary artery disease, peripheral vascular disease and congestive heart failure. The company's global brands, which are sold in approximately 100 countries, include Carpentier-Edwards, Cosgrove-Edwards, Swan-Ganz, and Fogarty. Additional company information can be found at www.edwards.com .

This news release includes forward-looking statements that involve risks and uncertainties, including those related to the success of preclinical and clinical studies of percutaneous heart valve replacement, the potential size of the catheter-based heart valve repair and replacement market, the potential for Edwards to

provide these technologies to non-surgical candidates even sooner, the ability of this transaction to further strengthen the company's global leadership, and, more generally, the ability to consummate targeted technology investments and acquisitions; timing or results of pending or future clinical trials, actions by the U.S. Food and Drug Administration and European Union, technological advances in the medical field, product demand and market acceptance, the effect of changing economic conditions, the impact of foreign exchange, and other risks detailed in the company's filings with the Securities and Exchange Commission. These forward-looking statements are based on estimates and assumptions made by management of the company and are believed to be reasonable, though are inherently uncertain and difficult to predict. Actual results or experience could differ materially from the forward-looking statements.

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EXHIBIT 3

AARHUS UNIVERSITET

HENNING RUD ANDERSEN

overlæge

Tlf: 8949 6111
E-post: henning.rud.andersen@ki.au.dk

Postadresse
Hjertemedicinsk Afdeling B, SKS
Skejby Sygehus
Brendstrupgårdsvej 100
8200 Århus N

- Publikationer
- Aktiviteter

Henvendelse om denne sides indhold: Telefonomstillingen eller Henning Rud Andersen
Genereret 06.02.2008

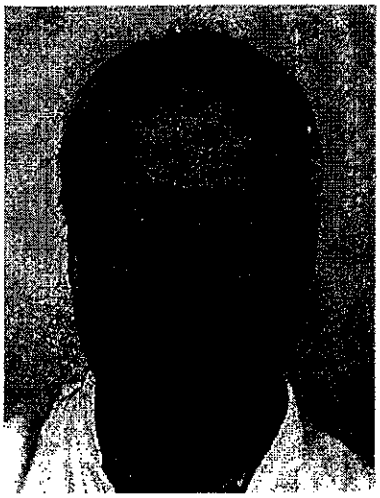
AARHUS UNIVERSITET

JOHN MICHAEL HASENKAM

professor, dr.med.

Tlf: 8949 5480
E-post: hasenkam@ki.au.dk

Postadresse
T-Forskning
Skejby Sygehus
Brendstrupgårdsvej 100
8200 Århus N



- Curriculum Vitae
- Publikationer
- Aktiviteter

Forskningsområder

Natur og matematik
Biologi ▸ **Dyrefysiologi** ▸ Biomedicinsk teknik · Cavitation · Giraffens blodkredsløb · Hæmodynamik · Kunstige hjerteklapper · Lyd fra kunstige hjerteklapper · Myokardie iskæmi · Normale hjerteklapper · Syge hjerteklapper · Venstre ventrikel dysfunktion

Sundhed og sygdom
Forsknings- og undersøgelsesmetoder ▸ **Billeddannende undersøgelser** ▸ Biomedicinsk teknik · Giraffens blodkredsløb · Hæmodynamik · Kunstige hjerteklapper · Myokardie iskæmi · Normale hjerteklapper · Syge hjerteklapper · Venstre ventrikel dysfunktion
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Forsknings- og undersøgelsesmetoder ▸ **Blod** ▸ AK-behandling - selvstyret · Biomedicinsk teknik · Cavitation · Hæmodynamik · Kunstige hjerteklapper · Lyd fra kunstige hjerteklapper · Syge hjerteklapper
Forsknings- og undersøgelsesmetoder ▸ **Hjerte og kredsløb** ▸ AK-behandling - selvstyret · Biomedicinsk teknik · Cavitation · Giraffens blodkredsløb · Hæmodynamik · Kunstige hjerteklapper · Lyd fra kunstige hjerteklapper · Myokardie iskæmi · Normale hjerteklapper · Syge hjerteklapper · Venstre ventrikel dysfunktion
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Sygdomsforebyggelse ▸ **Blod** ▸ AK-behandling - selvstyret · Hæmodynamik · Kunstige hjerteklapper
Sygdomsforebyggelse ▸ **Hjerte og kredsløb** ▸ AK-behandling - selvstyret · Hæmodynamik · Kunstige hjerteklapper

Henvendelse om denne sides indhold: Telefonomstillingen eller John Michael Hasenkam
Genereret 15.02.2008

AARHUS UNIVERSITET

LARS KNUDSEN

afdelingslæge

E-post: lknud@as.aaa.dk

Postadresse
Anæstesiologisk Afdeling, NBG
Århus Sygehus
Nørrebrogade 44
8000 Århus C

- Publikationer

Henvendelse om denne sides indhold: Telefonomstillingen eller Lars Knudsen
Genereret 06.02.2008

EXHIBIT 4

European Heart Journal (1992) 13, 704–708

Transluminal implantation of artificial heart valves. Description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs

H. R. ANDERSEN*, L. L. KNUDSEN* AND J. M. HASENKAM†

*Departments of *Cardiology, †Thoracic and Cardiovascular Surgery, and the Institute of Experimental Clinical Research, Skejby University Hospital, Aarhus, Denmark*

KEY WORDS: Expandable stent–valve, transluminal implantation, prosthetic heart valve, pigs.

A new artificial aortic valve prosthesis was developed for implantation by the transluminal catheter technique without thoracotomy or extracorporal circulation. The new heart valve was prepared by mounting a porcine aortic valve into an expandable stent. Before implantation, the stent–valve was mounted on a balloon catheter and compressed around the deflated balloon. The stent–valve mounted balloon catheter was then advanced retrogradely to the ascending aorta or the aortic root in anaesthetized pigs. Implantation was performed by balloon inflation which expanded the stent–valve to a diameter exceeding the internal diameter of the vessel — thus ensuring a stable fixation against the vessel wall. A total of nine implantations were performed in seven 70 kg closed chest pigs. Sub- and supracoronary implantation was performed in two and three pigs, respectively, while implantation in both positions was done in two. Angiographic and haemodynamic evaluation after implantation revealed no significant stenosis (≤16 mmHg) in any of the nine valves and trivial regurgitation in only two. Complications were associated with restriction of the coronary blood flow in three animals. This preliminary study indicates that artificial aortic valves can be implanted in closed chest animals by transluminal catheter technique.

Introduction

In 1952, Hufnagel and Harvey[1] performed the first implantation of a prosthetic heart valve in a patient with severe aortic regurgitation. The artificial valve was implanted in the descending thoracic aorta and prevented severe regurgitation to the left ventricle[2]. This technique was used in small series of operations for aortic regurgitation[3,4]. The development of extracorporal circulation made it possible for Harken *et al.* to perform the first subcoronary implantation in 1960[5], and since then, implantation of prosthetic heart valves has been an open heart surgical procedure. If, however, implantation could be accomplished without thoracotomy, it would be attractive.

In 1989, we constructed a new artificial heart valve designed for implantation by transluminal catheter technique without thoracotomy and heart surgery[6]. This paper describes the new prosthetic heart valve, the implantation technique, and the initial preliminary results with implantation in the sub- and supracoronary position in pigs.

Material and methods

A NEW CONCEPT FOR IMPLANTATION OF ARTIFICIAL HEART VALVES

The idea was conceived of mounting a foldable biological cardiac valve inside a balloon expandable metalic stent. Implantation of such a device (stent + valve = the stent–valve), would enable implantation of artificial heart valves by the transluminal catheter technique.

The stent was constructed of two 0·55 mm surgical stainless steel wires (monofilament), each folded in 15 loops (Fig. 1(a)). Three of the loops were 14 mm high, designed to the commisures of a porcine aortic valve. The remaining loops in the first wire and all the second wire loops were 8 mm high. Each folded wire was bent into a circle (diameter, 22 mm) which was closed end-to-end by soldering. The two circles were then stacked upon each other and interfixed by Merseline 2-0 sutures (Fig. 1(a)).

The foldable valve was a porcine aortic valve taken from a 90 kg slaughtered pig (mixed Danish Landrace and Yorkshire). The aortic valve was carefully dissected and cleaned manually to remove unwanted material. The diameter, thickness, and height of the cleaned valve annulus was 27 mm, 1 mm, and 2 mm, respectively. The height of the three commisural sites were 8 mm.

The stent–valve was prepared by mounting the cleaned aortic valve inside the stent (Fig. 1(b) and (c)). The aortic annulus, which included the three commissural sites, were fixed to the metalic stent by 45–50 Prolene 5-0 sutures. The external diameter of the stent–valve was approximately 12 mm when collapsed (Fig. 1(d) and (e)), and 32 mm when entirely expanded (Fig. 1(f) and (g)). After the stent–valve had been manually compressed on the carrier balloon catheter, the stiffness of the metal prevented it from uncoiling spontaneously (Fig. 1(d) and (e)). After expansion, the stiffness of the metal minimized spontaneous recoil, when the balloon was deflated (Fig. 1(f) and (g)). However, a small recoil (< 10% diameter

Correspondence. Henning Rud Andersen, MD, Department of Cardiology, Skejby University Hospital, Brendstrupgaardsvej, DK-8200 Aarhus N, Denmark.

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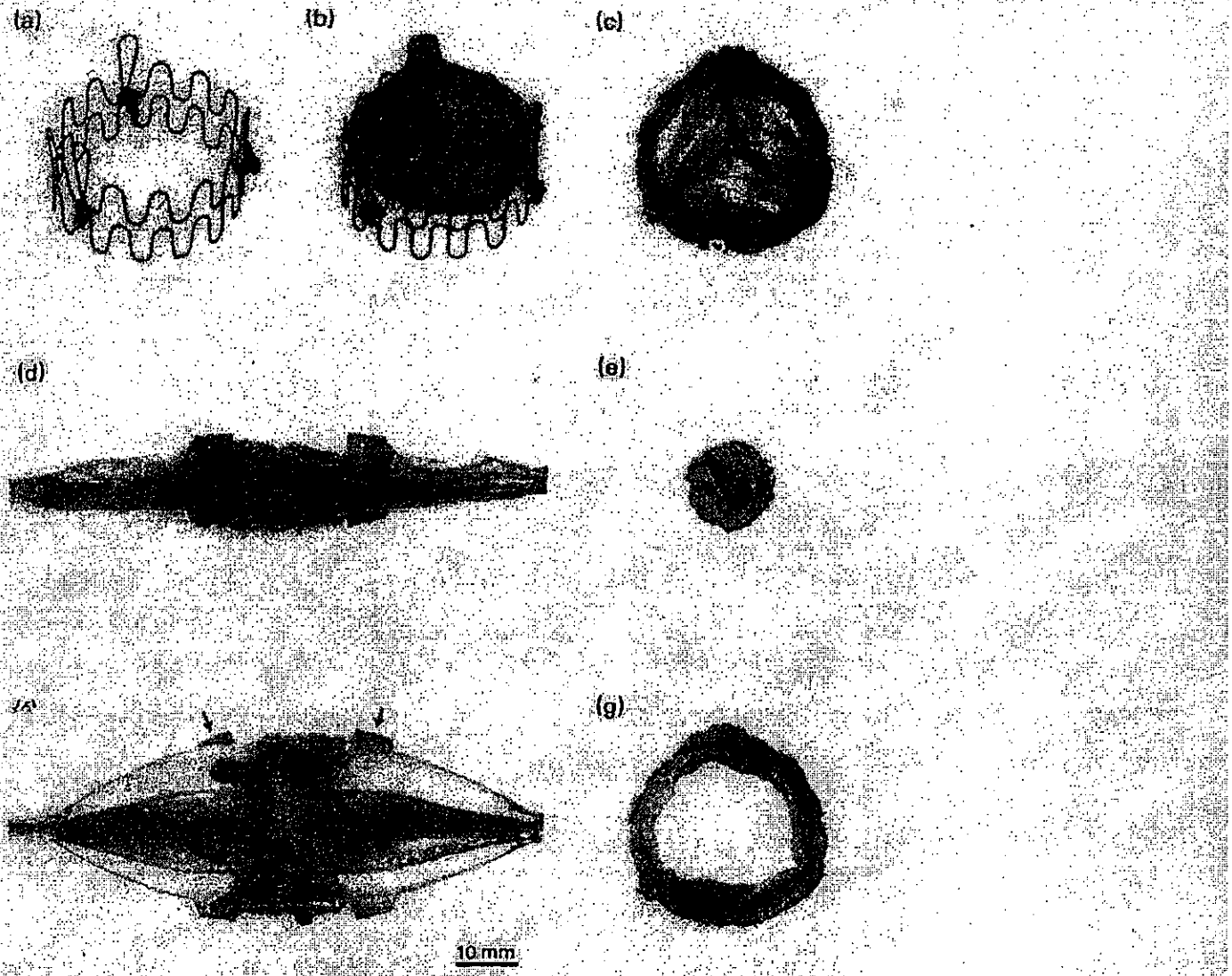

Figure 1 The stent was constructed with two 0·55 mm stainless steel wires folded in 15 loops (a). A three-leaflet porcine aortic valve was mounted inside the stent and fixed to the metal by sutures to form the stent–valve (b) and (c). Before implantation the stent–valve was mounted on a deflated three-foiled balloon dilatation catheter (d). The diameter of the collapsed stent–valve was 12 mm (d) and (e). Balloon inflation expanded the stent–valve to an external diameter of 32 mm (f) and (g). Each of the three balloons were mounted with two elastic blocks (indicated by arrows), to prevent migration of the stent–valve from the middle of the balloons.

reduction) was often seen during balloon deflation. After preparation, the stent–valves were kept frozen (−20 °C) until implantation some days later. Since only acute studies were performed in this initial phase, the valves were neither sterilized, heparinized nor treated by drugs or chemical agents.

The carrier balloon catheter used for implantation was a conventional No. 12 F three-foiled aortic valvuloplasty balloon dilatation catheter (Schneider, Zürich, Switzerland). Each of the three balloons was 70 mm long and had a diameter of 15 mm. The total diameter of the three balloons were 31 mm when inflated. Two soft rubber blocks (3 mm high) were mounted on each of the three balloons, separated by a distance of 18 mm (Fig. 1(d) and (f)). The blocks ensured the stent–valve's stable position in the middle of the balloons, and avoided migration during catheter advancement and balloon inflation. The carrier balloon catheter was mounted in a self-constructed No. 41 F flexible introducer sheath (external diameter 13·6 mm, internal diameter 12·5 mm, length 75 cm). The stent–valve loaded carrier balloon catheter was retracted into the introducer sheath during intravascular introduction and advancement to minimize friction against the vessel wall. A standard guidewire, 300 cm long and 0·9 mm in diameter, was used for conventional catheter-over-guidewire advancement of the carrier balloon catheter.

ANIMAL PREPARATION

Seven pigs weighing 70 kg (mixed Danish Landrace and Yorkshire) were used for implantation. The animals were anaesthetized, endotracheally intubated, and ventilated artificially. Surface ECG and blood pressures were recorded on a Sirecust 961 Monitor (Siemens AG, Erlangen, Germany) and on paper by a Mingograph-62 ink-jet galvanometer recorder (Siemens, Stockholm, Sweden). A No. 9 F introducer sheath was placed in the right carotid artery after surgical exposure of the vessel. A No. 8 F pigtail catheter was advanced to the ascending aorta through the sheath, and used for pressure monitoring and for angiography. After stent–valve implantation, the pigtail catheter was exchanged with a No. 8 F multipurpose coronary arteriography catheter with an open end-hole which was advanced retrogradely through the stent–valve, and used for pressure measurements. A No. 12 F Foley balloon catheter (Rüsch, Kernen, Germany) with a balloon diameter of 40 mm was introduced into a neck vein, and advanced to the pulmonary trunk guided by fluoroscopy. The balloon could be inflated to decrease blood flow through the lungs and consequently through the left ventricle. This was used to minimize the high blood velocities past the valve prosthesis, causing pulsatile movements of the carrier balloon catheter during stent–valve implantation in the heart.

Because the femoral arteries of 70-kg pigs are only 3–4 mm in diameter, retroperitoneal access to the abdominal aorta was made through a midline laparotomy. The aorta was exposed over a distance of 6–7 cm cranial to the renal arteries and cross-clamped proximally and distally. During temporary cross-clamping, a 4 cm long incision enabled a 8–10 cm long vascular prosthesis (diameter 20 mm), to be sutured end-to-side to the aorta at an angle of 45°. The prosthesis was used to gain intravascular access for the No. 41 F introducer sheath. The animals were given no antiplatelet or anticoagulant drugs, and after implantation, angiography and pressure measurements, the pigs were exsanguinated under continuous anaesthesia.

IMPLANTATION OF THE STENT–VALVE

The guidewire was advanced retrogradely into the left ventricle under continuous fluoroscopy, and subsequently, the introducer sheath was advanced over the guidewire into the descending thoracic aorta. The carrier balloon catheter was then pushed out from the sheath and advanced further around the aortic arch. For supracoronary implantation, the stent–valve was positioned just beneath where the right brachiocephalic artery started. For subcoronary implantation the stent–valve was positioned in the aortic root/left ventricular outflow tract beneath the coronary arteries at the level of the native aortic valve. The position of the stent–valve was guided by transthoracic echocardiography and fluoroscopy in the initial four pigs. Due to inaccuracy of echocardiography (heavy echoes from the stent), the implantations in the subsequent three pigs were guided by fluoroscopy and angiography. In these three experiments, ventriculography and aortography were recorded on videotape for immediate playback to guide the stent–valve implantation. When the stent–valve was placed in the right position, implantation (stent–valve expansion) was performed by balloon inflation (4 atmospheres in 15 s) which overdilated (overstretched) the vessel. The elastic recoil of the vessel secured fixation and minimized periprosthetic leakage. Subsequently, the deflated balloon catheter, the guidewire, and the sheath were withdrawn. Two pigs were exposed to double stent–valve implantation with the first one implanted in the supracoronary position; the second stent–valve was advanced retrogradely through the first valve and implanted in the subcoronary position.

MEASUREMENTS AFTER IMPLANTATION

Pressure measurements were performed immediately after implantation. Measurements were obtained during slow withdrawal of the catheter from the left ventricle to the aortic arch distal to the stent–valve. Afterwards, ventriculography and aortography were obtained by contrast injection through the pigtail catheter (Fig. 2). Following exsanguination, the heart and the aorta were excised and gross pathological examination was performed.

Results

THE IMPLANTATION PROCEDURE

The introducer sheath was easily inserted through the vascular prosthesis and advanced to the thoracic aorta guided by fluoroscopy. Before balloon inflation (stent–valve expansion) the carrier balloon was kept easily in a stable position in the blood-stream. When the carrier balloon was inflated, the blood-flow carried it approximately another 3–4 mm distally (downstream). The pulmonary artery balloon was inflated in two pigs, both with subcoronary implantation, because of pulsatile movements of the carrier balloon. The blood-flow could be totally obstructed for a short period (10–15 s, if needed), or decreased for a longer time (min). The latter method was used in two animals (Nos 5 and 6). Seven pigs had nine stent–valves implanted (four in the subcoronary and five in the supracoronary position; Table 1).

HAEMODYNAMICS AND ANGIOGRAPHY

All the animals survived the initial post-implant period; and pressure measurement and angiography was accomplished (Table 1). None of the stent–valves caused severe stenosis and only trivial contrast regurgitation was seen in two pigs (Nos 1 and 3). Left ventricular end-diastolic pressures were unchanged after stent–valve implantation in five out of seven pigs, but increased in two (Nos 3 and 4) due to left ventricular failure caused by restriction of the coronary blood-flow.

ANATOMICAL FINDINGS

All nine prosthetic valves were undamaged by the implantation procedure, and the sutures kept the biological valves inside the stents stable. No haematoma, bleeding or aortic dissection was seen in any of the seven pigs. Four pigs, in which no mechanical complications were

Figure 2 Angiography showing stent–valves (indicated by arrows) implanted in subcoronary position (a) and supracoronary position (b). ao: aorta, LV: left ventricle.

Table 1 Blood pressure measurements following stent–valve implantation

Pig no	Survival (h)	Site of implantation		Blood pressure (mmHg)			
		Subcoronary	Supracoronary	Left ventricle	Above subcoronary stent–valve	Below supracoronary stent–valve	Above supracoronary stent–valve
1	2·5	+	+	100/0	100/60	100/60	100/60
2	2·5		+	120/7	—	105/75	105/75
3	0·25	+		64/30	60/35	—	—
4	0·25		+	43/18	—	—	40/17
5	1·5	+		150/−5	134/97	—	—
6	2·5	+	+	110/0	100/60	102/58	103/58
7	2·0		+	115/6	—	100/57	100/57

seen, fulfilled the study's protocol. In three animals, the coronary flow was restricted.

With supracoronary implantation, all five stent–valves were fixed in the ascending aorta; the aortic diameter was overstretched by 3–4 mm. Four of the five stent–valves were positioned more than 1·5 cm above the genuine valves; none of the valves obstructed the brachiocephalic artery. In one animal (No. 4), in which the stent–valve was implanted 3 mm above the native aortic valve, the stent–valve was competent, thus leaving only a small volume of blood between the native valve and the stent–valve available for coronary flow in diastole. This caused ST elevation and pump failure. All the stent–valves were competent at inspection and without coagulated blood on the cusps. However, small thrombi were seen on the metal and sutures.

With subcoronary implantation, all stent–valves were implanted at the level of the genuine valves which were completely compressed between the metal stent and the vessel/heart wall. Two of the four stent–valves were implanted beneath the origin of the coronary arteries. The other two (Nos 3 and 5) restricted coronary flow. In pig No. 3, both coronary arteries were obstructed, and the pig died due to pump failure. In pig No. 5 the left coronary ostium was free of the stent–valve, but the right coronary artery was partially obstructed. This animal was haemodynamically stable, but died suddenly from ventricular fibrillation 1·5 h after implantation. Mild regurgitation at aortography was found in two stent–valves. This was caused by tightness of one of the stent-valve cusps in one case (probably caused by the preparation), in the other there was a small paraprosthetic leak.

Discussion

IMPLANTATION OF PROSTHETIC HEART VALVES WITHOUT THORACOTOMY

This paper presents the first description and preliminary results of a new expandable artificial heart valve designed for permanent implantation by transluminal

catheter technique without thoracotomy. Catheter-mounted valves have previously been constructed for short-term treatment of acute aortic insufficiency[7,8]. These devices were mounted on long catheter wires which extended out through the vessel wall. Their position in the bloodstream was secured by external fixation of the extending catheter wires to the skin. Consequently, such valves were not suitable for permanent implantation. In contrast, the new stent–valve is fixed intravascularly at the site of implantation without stent material projecting into the bloodstream or penetrating the vessel wall, thus making it more suitable for permanent implantation.

THE STENT–VALVE

The present devices were self-constructed from available materials. The 0·55 mm wire fulfilled the criteria of minimal spontaneous 'uncoil' and 'recoil' after compression and dilatation. If the metal loops were longer than 8 mm, it was much easier to dilate the stent, but this resulted in larger deformation by the opposing elastic recoil from the vessel and/or the heart. If the loops were smaller, the stent was too stiff to be fully expanded by the balloon. We used biological valves, because they were easy to obtain and mount inside the stent. Other types of foldable valves may also prove suitable, e.g. the tricuspid polyurethane heart valve[9,10].

THE IMPLANTATION PROCEDURE

The extrathoracic approach was mandatory. As femoral arteries are very small in pigs we chose the abdominal aortic route for catheterization. Obviously, the femoral route should be used in humans, preferentially by a percutaneous approach, alternatively by arteriotomy. Implantation was easy in both the ascending and descending aortas[6] where small movements of the carrier balloon catheter were not critical. However, with subcoronary implantation such movements proved to be a problem. A catheter which does not obstruct the blood-flow during stent–valve expansion could be the solution.

LIMITATIONS OF THE STUDY AND FUTURE TECHNICAL DEVELOPMENTS

This is a very preliminary technical study, and many important questions remains to be answered about the stent–valve. Since only acute studies were performed the long-term durability of the valve is unknown. Questions regarding neointimalization, calcification, thrombogenicity, and dislodgement during long-term follow-up should be addressed. There may be a risk of dislodgement and distal migration due to long-term gradual dilation or even necrosis of the portion of the aorta where the valve is implanted. Furthermore, valvular or aortic pathology, such as calcium, vegetative debris, fibrosis, and abscess formation could prevent accurate fixation or become a source of embolization. Thus, many more complex and long-term animal studies must be performed before even speculation concerning clinical use is begun.

POSSIBLE CLINICAL IMPLICATIONS

This preliminary feasibility study cannot clarify the clinical applicability of the stent–valve. However, it might be a treatment for patients with aortic regurgitation who are not candidates for open heart surgery. Implantation of the stent–valve in a supracoronary position may protect the left ventricle from severe regurgitation[1–4].

This study was supported by a grant from the Danish Heart Foundation, Copenhagen, Denmark.

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EXHIBIT 5

the international JOURNAL OF ARTIFICIAL ORGANS

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Artificial Heart and Cardiac Assist Devices

Catheter-implanted prosthetic heart valves

Transluminal catheter implantation of a new expandable artificial heart valve in the descending thoracic aorta in isolated vessels and closed chest pigs

L.L. KNUDSEN[1], H.R. ANDERSEN[1], J.M. HASENKAM[2]

[1] Department of Cardiology, and
[2] Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus, Aarhus University Hospital, and Institute of Experimental Clinical Research, Aarhus University, Aarhus - Denmark

ABSTRACT: A new expandable artificial heart valve was developed for implantation by a transluminal catheter technique without using thoracotomy or extracorporeal circulation. The aim of this study was to implant the valve in isolated vessels of the descending thoracic aorta as well as in closed chest pigs, and furthermore to study the prosthesis' mechanical stability and the valve function. The artificial valve was made by mounting a porcine aortic valve on an expandable stent. Before implantation, the stent-valve was compressed on a deflated balloon catheter and mounted inside an introducer sheath. After intravascular introduction to the descending thoracic aorta the stent-valve was discharged from the sheath. Implantation was performed by balloon inflation which expanded the stent-valve to a diameter exceeding the internal vessel's diameter. After balloon deflation the stent-valve maintained an expanded configuration ensuring a stable fixation against the vessel wall. In vitro *implantations were performed in 36 isolated descending thoracic aorta specimens obtained from 80 kg pigs. Mechanical stability was evaluated by applying a downing load to the prosthesis. No displacement occurred at loads ≤ 1 kg when a large balloon (31 mm) was used for implantation. Transvalvular pressure differences between 11-47 mmHg (median) were obtained at antegrade flowrates between 5-8 l/min. Furthermore, only moderate leakage flows were measured during retrograde perfusion.* In vivo *implantations were performed in six 80 kg pigs. Implantation was safe and easy, and angiograph and haemodynamic evaluations revealed essentially no stenosis or regurgitation. No complications in migration, perforation, hemorrhage or thrombosis were observed. This study indicates a good mechanical stability and valve function of the new expandable artificial valves. (Int J Artif Organs 1993; 16: 253-62)*

KEY WORDS: Heart valve prosthesis, Stent-valve, Transluminal implantation, Pigs

INTRODUCTION

Implantation of an artificial heart valve as a treatment for valvular heart disease dates back to 1952, when Hufnagel performed the first implantation in a patient with severe aortic insufficiency (1). The artificial heart valve was implanted in the descending thoracic aorta and diminished severe left ventricular regurgitation and improved hemodyanmics (2-4). Follow-up reports twenty-five years later of subsequent operations revealed satisfactory results (2). The introduction of extracorporeal circulation and cardioplegic arrest permitted subcoronary implantation (5), and since then artificial heart valve implantation has been

The Authors are affiliated to The Cardiovascular Research Center, Aarhus University, Aarhus - Denmark

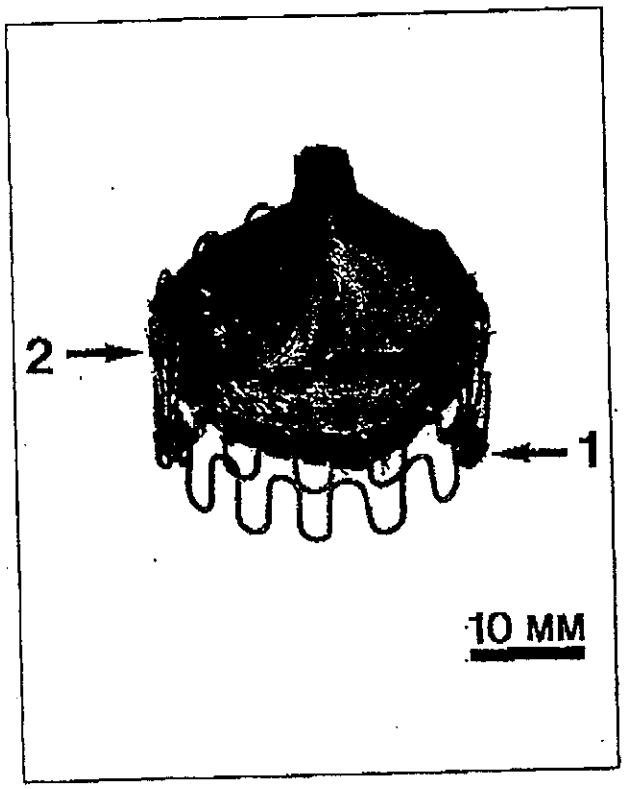

Fig. 1 - *Photograph of the stent-valve made of two metal rings which were interfixed by sutures (arrow 1) and a porcine aortic valve mounted inside the stent. The valve was fixed to the stent by sutures (arrow 2).*

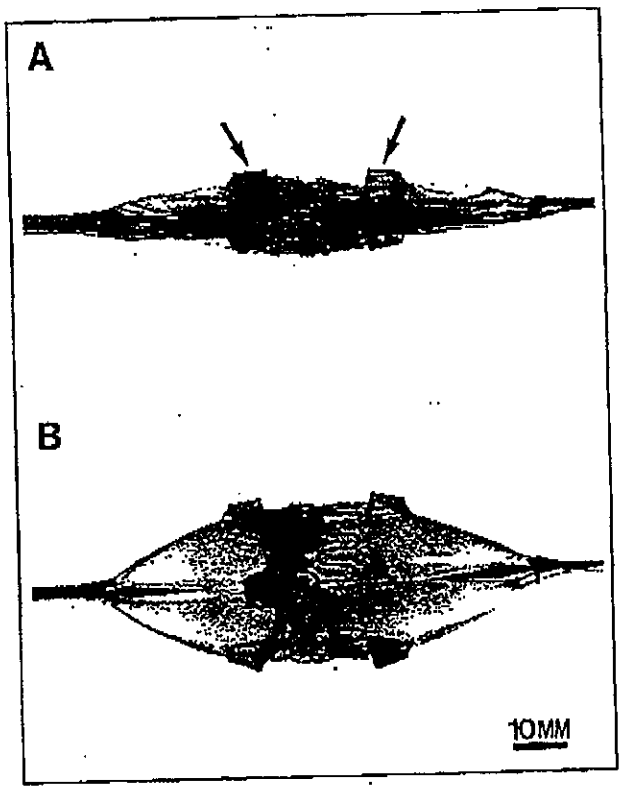

Fig. 2 - *Photographs of the balloon-mounted stent-valve placed between the tapered elastic blocks (arrows). The stent-valve's diameter was 12 mm when mounted on a deflated balloon* (A) *and 30 mm on the inflated balloon* (B).

an open heart surgical procedure. However, in some patients implantation accomplished without thoracotomy would be an attractive and a less extensive treatment.

We constructed a new artificial heart valve designed for implantation by using a transluminal catheter technique without thoracotomy and open heart surgery (6). The present study describes the first preliminary results with *in vitro* and acute *in vivo* descending thoracic aorta implantations in pigs.

MATERIALS AND METHODS

The concept

We conceived the idea of mounting a foldable biological cardiac valve inside a balloon expandable metal stent. Implantation of such a device (stent + valve = stent-valve) would enable artificial heart valve implantation by using the transluminal catheter technique.

The stent-valve

The stent-valve (Fig. 1) was made of a porcine aortic valve mounted inside an expandable stent. The valves were obtained from 90 kg pigs, and dissected free from the aortic wall and the septal myocardial shelf. The stent construction was essentially comprised of two metal rings fitted one upon the other and fixed by Merseline® 2-0 sutures. Each ring was made of a 0.55 mm monofilament stainless steel wire bent in 15 loops and soldered end to end. Three of the loops were expecially designed for fixation of aortic valve commissures, which was fixed inside the stent by 45-50 Prolene® 5-0 sutures. For preservation the stent-valve was kept frozen (-20°C) until implantation

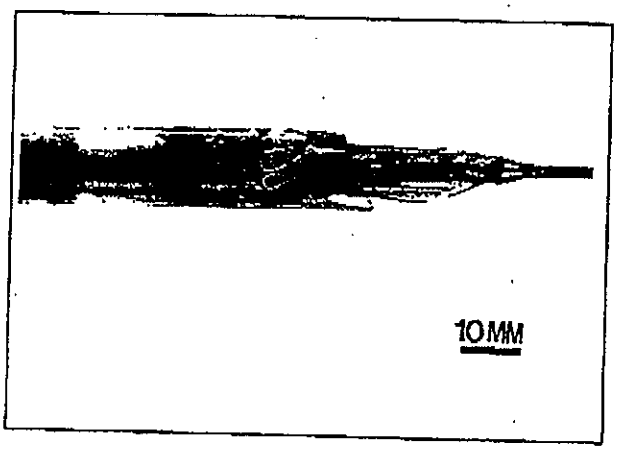

Fig. 3 - *Photograph of the balloon-mounted stent-valve retracted into the introducer sheath.*

some days later, and was neither treated by drugs nor chemical agents.

The balloon-mounted stent-valve

A conventional threefoil aortic valvuloplasty balloon dilatation catheter (Schneider, Zurich, Switzerland) was used (Fig. 2). Two elastic tapered blocks were glued on each balloon foil. The stent-valve was mounted on the deflated balloon catheter and manually compressed between the blocks, which ensured a stable positioning and avoided migration of the stent-valve. Balloon inflation expanded the stent-valve (Fig. 2B) and after subsequent balloon deflation the stent-valve maintained an expanded configuration.

The introducer sheath

An introducer sheath was constructed to accommodate the stent-valve mounted on the aortic balloon dilatation catheter. The sheath was composed of two 75 cm long catheters telescoping one into another. The outermost catheter contained a 65 cm long flexible plastic tube with a rigid acryl tube at the tip. The acryl tube contained the stent-valve during intravascular introduction and retrograde advancement (Fig. 3). The inner catheter was used for discharging the balloon-mounted stent-valve from the sheath. The introducer sheath had an external diameter of 13.6 mm and an internal diameter of 12.5 mm.

In vitro *studies*

Experimental set-up

Thirty-six descending thoracic aorta specimens were obtained from slaughtered 80 kg pigs. The specimens were dissected free of excessive tissue, and kept frozen (-20°C) until used some days later. At implantation, a no-flow constant pressure of 100 mm Hg was maintained inside the aortic specimens by using a liquid filled catheter connected to a 0.9% saline solution infusion bag. This was used to distend the vessel during vessel diameter measurements before and after implantation as well as during prosthesis stability measurements. The stent-valves were mounted on two different sized deflated trefoil balloon dilatation catheters. In the inflated state the balloons had a diameter of 25 mm (3 x 12 mm) and 31 mm (3 x 15 mm), respectively. The balloon-mounted stent-valves were inserted into the lumen of the aortic specimens and implantation was performed by a single dilatation of 4 atmospheres for 15 seconds. The specimens were continuously moistened in 0.9% saline. The implanted stent-valves were divided into two groups of 18, each conditioned by the two different sized balloons.

The external diameters of the vessels at the implantation site were measured before and after implantation to determine the vessel's degree of overstretching.

Prosthesis stability was determined by increasing the axial load on the stent-valve until displacement occurred. The aortic specimen containing the implanted stent-valve was hung up on a stand by two purse string sutures (Fig. 4). Three separate wires connected the commissural sites of the metal stent to the top part of a metallic disc, which also had a hinge for weight loading. An axial loading of 0.5, 1, 1.5 and 2 kg was used. Axial loading took place starting out with 0.5 kg and successively increased by 0.5 kg every three hours. Displacement was defined as migration of the stent-valve more than 2 mm.

Transvalvular pressure losses were obtained in a simple flow loop where the specimens were perfused with room temperature tap water (Fig. 5). The water was circulated by a roller pump (Polystan Type WM) which yielded a slightly pulsating flow ranging from 0 to 8.0 liters/min. The flow calibration was measured manually by a graduated cylinder and a stopwatch

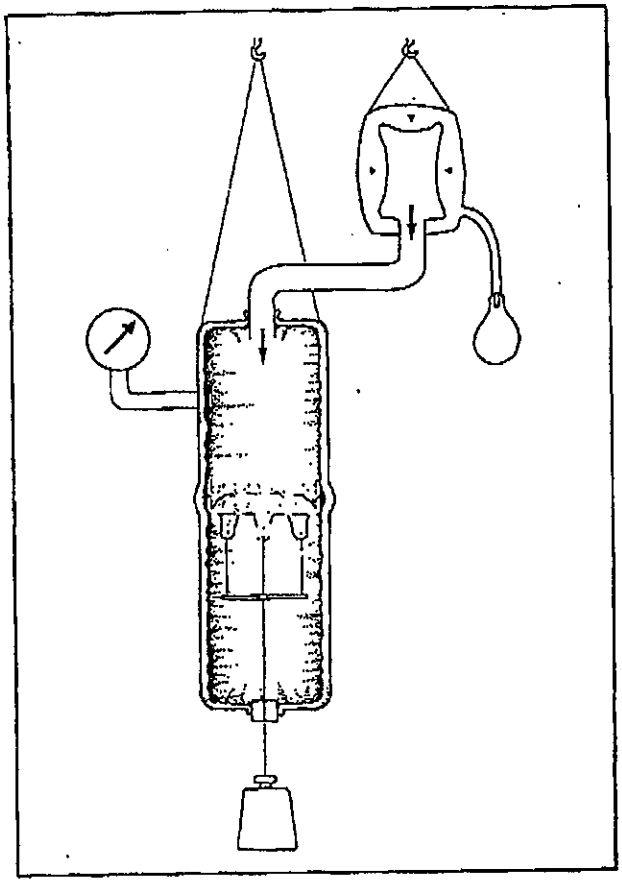

Fig. 4 - *A schematic drawing of the experimental set-up for measuring prosthesis stability. The stent-valve implanted in an aortic specimen was attached to a metallic disc and connected to an external axial load through a silicon occluder. Intraluminally, a constant pressure of 100 mmHg was maintained by a pressure infusion bag (thin arrow).*

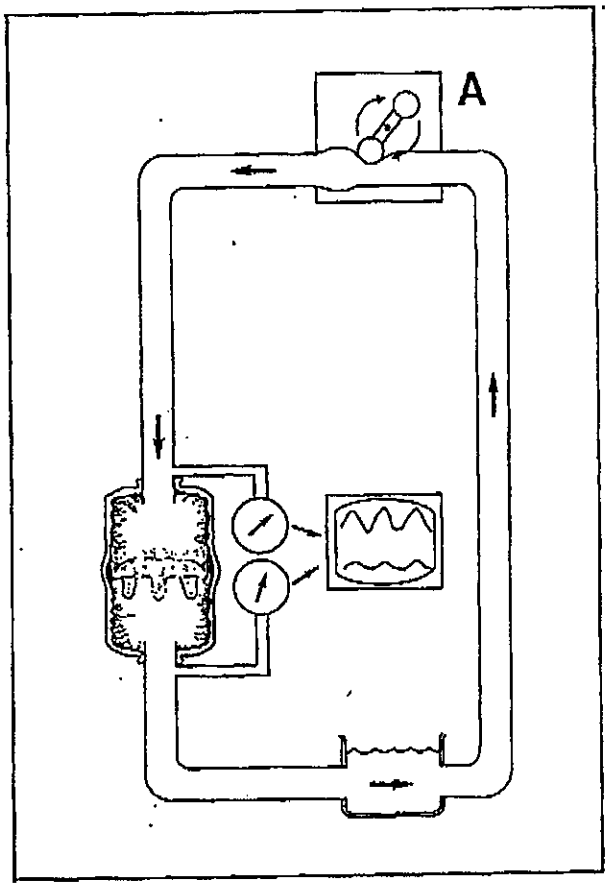

Fig. 5 - *A schematic drawing of the experimental set-up for transvalvular pressure measurements. An aortic specimen with an implanted stent-valve was placed in circulation which was driven by a roller pump (A). Pressures were measured on each valve side during different flow rates (5-8 l/min) to determine the pressure drop. The flow's direction indicated by thick arrows.*

technique, while the circulation was fed from a reservoir. Peak transvalvular pressure was measured by liquid filled tubes positioned one diameter upstream and one diameter downstream of the stent-valve, and recorded on a bedside monitor (SIRECUST 961, Siemens AG, Erlangen, Germany) via a Medex® Inc. type MX900 Novasensor pressure transducer (Medex, Rossendale, England). The diameter of the inlet and outlet tube was 13.5 mm and the inlet flow length was 2.0 meters. No peripheral resistance or compliance elements were applied to the system.

Leakage flow was measured by measuring the fluid volume that leaked retrograde through the stent-valve (Fig. 6). A liquid filled catheter was connected to the aortic specimen above the implanted stent-valve. A constant pressure difference of 100 mm Hg across the stent-valve was ensured by maintaining the pressure above the valve at 100 mm Hg, and keeping the part below the valve wide open (0 mm Hg). For leakage flow measurements the specimen was hung up in a vertical position and the fluid was sampled in a graduated cylinder for periods of 60 seconds.

In vivo *study*

Animal preparation

Six 6 month old pigs (mixed Danish Landrace and Yorkshire) of both genders weighing 75-80 kg were

used in this study. Animal care was approved and in compliance with the Danish Inspectorate for animal experimentation concerning the use of laboratory animals. Initially, the animals were anaesthetized intramuscularly with midazolam (Dormicum®) 15 mg and ketamine (Ketalar®) 1000 mg. After intravenous injection with 500 mg of ketamine an oral endotracheal intubation was performed, and anaesthesia was maintained with 1% halothane, 60-70% nitrous oxide and 30-40% oxygen administered via a ventilator, (Engstrøm type ER 311). Furthermore, 250 μg of fentanyl (Haldid®) was injected intravenously with anaesthesia introduction and subsequently every half hour. No heparin or antiplatelet drugs were given. A 9 F introducer sheath was placed in the right carotid artery after surgical exposure, and a 8 F pigtail catheter was advanced to the descending aorta for pressure measurements and aortography. Rectal and skin temperature, surface ECG and blood pressures were recorded on a Sirecust 961 monitor and on a Mingograph-62® ink-jet recorder (Siemens, Stockholm, Sweden). Arterial pO_2, pCO_2, pH, oxygen saturation, HCO_3 and Hgb were measured intermittently on an ABL1 blood gas analyzer (Radiometer Copenhagen, Denmark). After investigation the animals were sacrificed by desanguination under continued anaesthesia and subsequently anatomically examined.

Using an unsterile procedure, retroperitoneal access to the abdominal aorta was achieved through a midline laparotomy. The abdominal aorta was dissected free to allow cross clamping above and below the renal arteries. A vascular graft (Cooley®, diameter 20 mm) was sutured on the aorta at a 45 degree angle with two continuous Prolene® 5-0 sutures for convenient intravascular access. An aortography was perfomed and recorded on video tape to identify the implantation site in the descending thoracic aorta.

Implantation technique

The introducer sheath contained the stent-valve mounted on a 31 mm³ (3 x 15 mm) aortic balloon dilatation catheter. Under continuous flouroscopy the sheath was advanced through the vascular graft into the thorax via the intravascular route over a 0.9 mm steerable standard guidewire to the implantation site. The balloon catheter-mounted stent-valve was discharged from the sheath and freed into the bloodstream (Fig. 7A). A single dilatation to 4 atmospheres

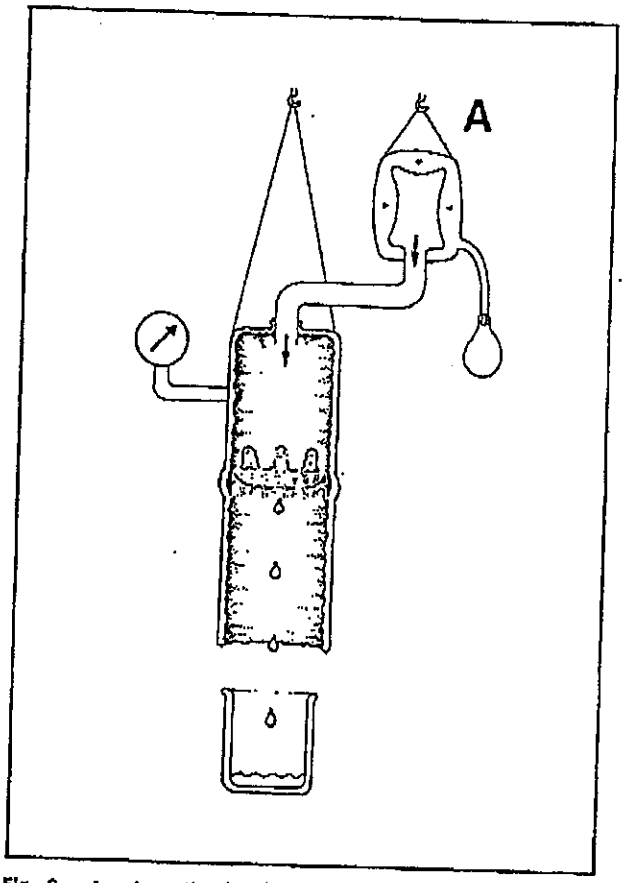

Fig. 6 - *A schematic drawing of the experimental set-up for leakage flow measurements. A constant pressure difference of 100 mmHg was maintained across the stent-valve by a pressure infusion bag (A). The arrows indicate the flow's direction.*

for 15 sec expanded the stent-valve to a diameter exceeding the internal diameter of the vessel by 3-4 mm and thereby ensuring a stable fixation against the vessel wall (Fig. 7B). Subsequently the balloon was deflated and withdrawn leaving the stent-valve in place (Fig. 7C).

Measurements

Pressure measurements were obtained proximally and distally to the stent-valve immediately after implantation. Eventually, aortography was made by contrast injection (35-50 ml/second) proximal and distal to the stent-valve and recorded on videotape (Fig. 8A+B). Stent-valve incompetence (evaluated qualitatively by contrast regurgitation) and the vessel pattern were observed. The angiographic diameter of the

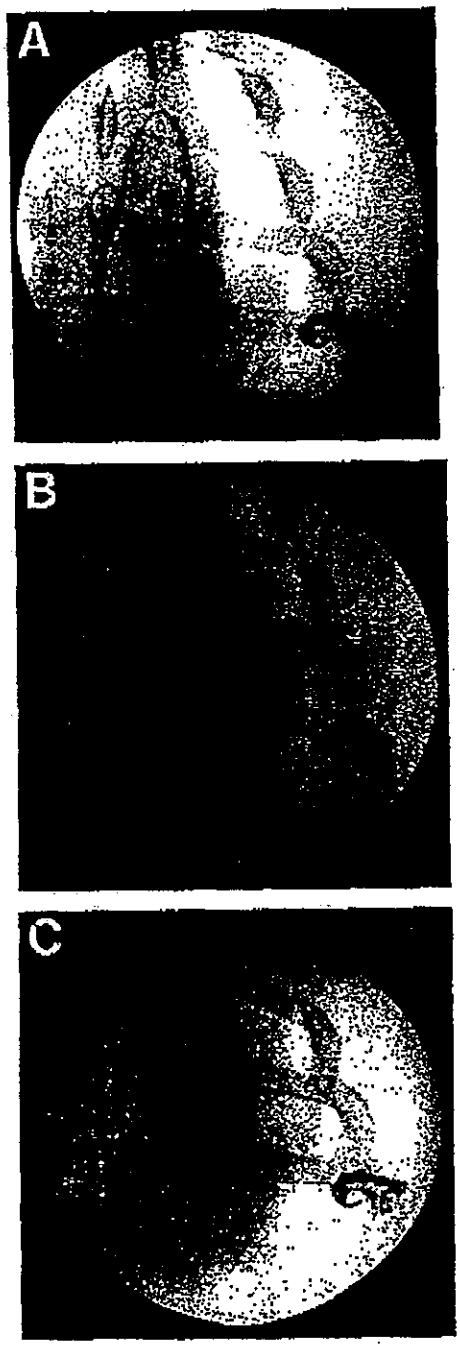

Fig. 7 - X-ray's of the in vivo implantation procedure in the descending thoracic aorta. (A) The balloon-mounted stent-valve before balloon inflation. (B) Stent-valve implantation by balloon inflation. (C) The stent-valve implanted and the balloon catheter retracted.

vessel before and after implantation was measured at the implantation site.

At autopsy the aorta and it's side branches were inspected and studied focusing on the implantation site, the stent-valve's position, stent-valve thrombosis and descending thoracic aorta perforation or dissection. Furthermore, the stent-valve fixation and the cusp function were evaluated. The heart weight and diameter of the excised stent-valve were measured.

RESULTS

In vitro *studies*

Stent-valves implanted with the 25 mm balloon overstretched the vessel by a median of 2.2 mm (range 2.0-2.5 mm) and those implanted with the 31 mm by 4.0 mm (range 3.5-4.5 mm). The spontaneous recoil of the vessel and the stent-valve during the balloon's deflation was less than 10%.

Prosthesis stability

The six stent-valves implanted with the 31 mm balloon revealed no displacement at 1/2 and 1 kg of loading, but one stent-valve was displaced at a 1 1/2 kg load. The remaining five stent-valves were displaced at loading of 2 kg.

The six stent-valves implanted with the 25 mm balloon showed no displacement at a loading of 1/2 kg, but two were displaced at a loading of 1 kg and the remaining four were displaced at 1 1/2 kg. No stent-valve migration was observed during the *in vitro* flow studies.

Transvalvular pressure loss

In six stent-valves implanted with the 25 mm balloon and in six with the 31 mm balloon, peak transvalvular pressure losses increased exponentially with increasing flow (Tab. I). Peak transvalvular pressure losses were slightly lower by using the 31 mm balloon compared with the 25 mm (statistically non-significant).

Leakage flow

Leakage flow measured for six consecutive stent-valves implanted with the 31 mm and 25 mm balloon are listed in Table II. The results with the 31 mm balloon revealed a gradual decline in retrograde flow values during the study.

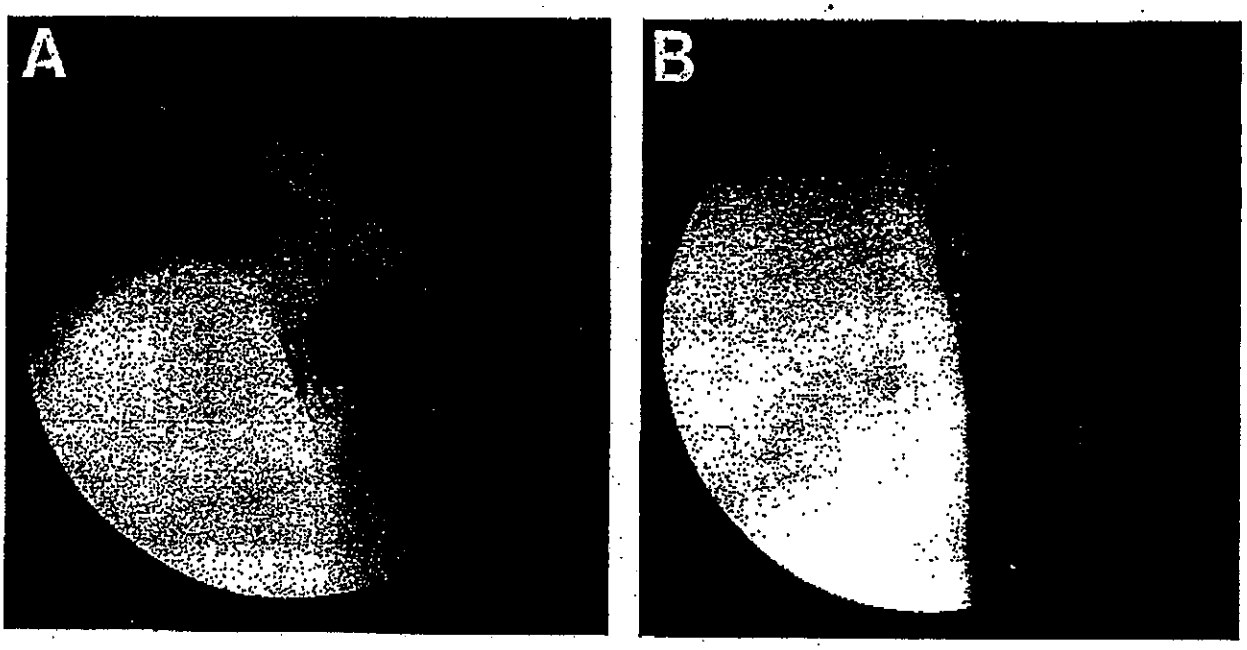

Fig. 8 – *Angiography showing the stent-valve implanted in the descending thoracic aorta.* (A) *Aortography above the stent-valve visualizes a wide open stent-valve which overstretched the vessel's internal diameter* (B). *Contrast injection below the stent-valve demonstrates a competent valve (no contrast regurgitation).*

In vivo *study*

Implantation procedure and technique

The anaesthetic and surgical procedures were uncomplicated in all cases. The introducer sheath was easily inserted through the vascular prosthesis into the abdominal aorta and advanced by conventional catheter over guidewire technique to the thoracic aorta guided by fluoroscopy. The balloon-mounted stent-valves were easily pushed out of the sheath. Six stent-valves were technically successful implanted in the descending thoracic aorta of 6 consecutive pigs. There were no device failures.

Angiography and hemodynamics

All animals survived the immediate postimplantion period and showed the same hemodynamic stability as prior to implantation. In all six pigs virtually no prosthesis stenosis (peak transvalvular pressure difference < 5 mm Hg) was found. Angiography demonstrated vessel patency with a measured overstretching of 3.5 mm at the implantation (range 3.0–4.0 mm) and widely patterned stent-valves with pliable cusps in all animals (Fig. 8A). No cases of angiographic evidence of trans- or periprosthetic regurgitation were observed (Fig. 8B). There was no vessel perforation, dissection, or migration of the stent-valve. The median time of in situ implantation was 2.0 hours (range 1.5–4 hours) until the animals were desanguinated in accordance with the protocol.

Postmortem examination

In accordance with the angiographic examination postmortem inspection revealed that all stent-valves were implanted in the descending thoracic aorta in axial position longitudinally to the vessel wall. The stent-valves were slightly embedded into the intima without gross thrombotic debris, perforation or hemorrhage. The prostheses were securely fixed and the cusps were undamaged. However, small thrombi were seen on the stent-valve's metal and sutures. The stent-valve median diameter was 22.5 mm (range 22–23 mm). The median heart weight was 350 g (range 320–370 g) with a calculated body weight fraction of 4.4 g/kg (range 4.3–4.6 g/kg).

TABLE I - *IN-VITRO* TRANSVALVULAR PEAK PRESSURE DIFFERENCES

Flow (l/min)	Pressure differences (mm Hg)		
	Aortic specimen before stent-valve implantation N = 12	Aortic specimen after stent-valve implantation balloon size 25 mm N = 6	Aortic specimen after stent-valve implantation balloon size 31 mm N = 6
5.0	3.5 (0-6)	20.0 (7-26)	11.0 (8-19)
6.0	7.5 (0-10)	29.5 (19-31)	14.0 (4-27)
6.5	5.5 (0-9)	25.5 (7-35)	21.0 (7-27)
7.0	3.5 (1-9)	33.5 (28-35)	26.0 (12-23)
8.0	3.5 (0-8)	62.0 (36-85)	47.0 (15-55)

The peak pressure differences were measured using the experimental circulation model illustrated in Figure 5. Figures in median and range.

TABLE II - *IN VITRO* LEAKAGE FLOW MEASUREMENTS

Stent-valve No.	Leakage Flow (ml/min)	
	Stent-valve implanted with a 25 mm balloon	Stent-valve implanted with a 31 mm balloon
1	243	270
2	215	280
3	220	211
4	208	224
5	211	195
6	210	210
Median	213	217

Leakage flows were measured using the experimental set-up illustrated in Figure 6.

DISCUSSION

This paper presents the first results of a new expandable artificial valve implantation by transluminal catheter technique in the descending aorta in isolated vessels and as acute studies in closed chest pigs.

The balloon-mounted stent-valve

The idea of mounting a foldable valve inside an expandable stent is new (6). We used porcine valves because they were foldable, easy to obtain, and easy to mount inside the stent. Other valve material may be used, e.g. polyurethane heart valves (7, 8).

Initial experiments revealed that the stent's appropriate dynamic mechanical properties in respect to uncoil and recoil after expansion and compression (9, 10) was achieved by using a 0.65 mm stainless steel wire. We chose the trefoil balloon because the inflated state's large diameter. However, the expanded shape of the stent-valve was reflected by the balloon's contour and consequently disclosed a slightly trigone-like configuration. This may increase the risk of developing pressure necrosis in the aortic wall at the stent-valve's most protruding parts and a leakage between the vessel and the less protruding parts. Obviously, other balloon shapes which result in a circular shaped prosthesis lumen may prove more suitable.

The in-vitro study

The aim of the simplified *in vitro* study was to provide initial data about the prosthesis stability and valve function. Although, the stent-valve proved to have good mechanical stability when tested in this model, further testing under dynamic conditions to simulate aortic distensibility and to apply alternating directions of the axial loading should be conducted. Normal pigs have hyperelastic non-atherosclerotic vessels (11, 12) which in this study ensured good prosthesis stability. However, human atherosclerotic vessels may comply otherwise, and should be tested as well. The measured transvalvular pressure differences contain inherent sources of error. Using a roller pump (no peak systolic pulsatile flow) and mounting the elastic aortic specimen in a non-elastic circulation

means that the peak transvalvular pressure gradients represent arbitrary figures. The leakage flow measurements indicated a fairly competent valve with only a small leakage flow (approximately 5% of the normal cardiac output). Regurgitation should also be evaluated under pulsatile flow conditions. Furthermore, the set-up does not enable distinction between transvalvular and paravalvular leakage. Therefore, more extensive *in vitro* fluid mechanical and physical evaluation of the stent-valve is required (13).

In vivo study

The extrathoracic approach was essential in this study. In the present study the abdominal aortic route was chosen for catheterization, because the caliber of the femoral arteries in pigs is very small (diameter 3-4 mm). Obviously, the femoral route should be used in humans either by percutaneously or surgical exposure. Retrograde advancement, positioning, and implantation in the descending thoracic aorta was easy and successful when guided by fluoroscopy and angiography obtained prior to implantation. Before balloon inflation it was easy to keep the balloon-mounted stent-valve in a stable position within the blood-stream. During inflation small pulsatile balloon movements were seen but not as extensively as for implantation in the ascending thoracic aorta and the aortic annulus (6).

Aortography demonstrated no contrast regurgitation despite the rapid contrast injection (35-50 ml/seconds) immediately downstream of the stent-valve. However, diastolic regurgitation in the thoracic aorta is insignificant when the native aortic valve is competent. Therefore, the haemodynamic performance of the stent-valve in respect to regurgitation should be studied in a model with severe aortic insufficiency (study in progress). A stable fixation of the stent-valve was ensured by overstretching the aorta by using the 31 mm balloon. Theoretically, fixation may be improved by stent-valve neoendotheliazation, as it has been observed with coronary stents (14-16). This aspect could obviously not be evaluated in these acute studies. By inspection the cusps were undamaged and without any thrombotic debris, but microscopy is necessary to demonstrate possible leaflet damage due to mechanical stress during balloon inflation. Small thrombi were seen on the stent and sutures. Although neointimaliazation of coronary stents seems to reduce the risk of thrombotic complications, long-term stent-valve implantation is required to evaluate whether continued anticoagulation is necessary.

Future requirements

Our self-constructed stent-valve, the balloon catheter, and the introduced sheath used in this study evidently require further development and refinement as well as long-term follow-up studies in laboratory animals before human application may be considered. The devices' dimensions have to be reduced for femoral intrusion. The material has to be optimized with respect to un- and recoil of the stent following balloon in- and deflation, and it has to minimize vessel and valve trauma as well as trombogenicity.

Possible clinical implications

The first surgical artificial heart valve implantations were performed in the descending thoracic aorta by Hufnagel (1) as a treatment of severe aortic valve insufficiency. Implantation of the Hufnagel valve claimed to reduce the total regurgitant flow by 75% and to normalize the pulse contour distal to the valve (3, 17, 18). Twenty-five years later some patients still had a satisfactorily functioning valve (2).

Transluminal stent-valve implantation may be a useful treatment in patients with severe aortic insufficiency who are not candidates for open heart surgery. Furthermore, in accordance with Hufnagel's ideas patients with aortic valve stenosis might benefit from placing the stent-valve in the descending aorta and then proceed with a balloon valvuloplasty to reduce the risks of developing a severe acute valve insufficiency.

It is possible to implant the stent-valve in the ascending aorta and in the subcoronary position (6). Although these positions are hemodynamically more beneficial they are also technically more difficult to perform and may imply a higher risk since instrumentation of an atherosclerotic aortic arch could increase the risk of cerebral emboli.

Evidently our results are preliminary. Further short-term and long-term follow-up studies must be performed in laboratory models to evaluate the feasibility of this new technique.

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Reprint requests to:
Dr. Henning Rud Andersen
Department of Cardiology
Skejby Sygehus, Aarhus University Hospital
DK-8200 Aarhus N
Denmark

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EXHIBIT 6

FDC REPORTS "The Gray Sheet"

MEDICAL DEVICES, DIAGNOSTICS & INSTRUMENTATION

November 21, 2005
Volume 31 | Number 047 | page 17

CoreValve Could Go Public In 2007, Readies Next-Gen Catheter For Europe

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Percutaneous aortic valve developer CoreValve says it is considering going public as an exit strategy instead of undertaking another round of financing.

Based on the ***ReValving*** system's preliminary clinical success and an "immense" potential market, the firm is now "strongly considering the initial public offering route as a strong possibility as an exit and capitalization strategy," CEO Jacques Séguin said.

CoreValve estimates the initial market size at 50,000-60,000 patients, those too ill to receive open heart surgery.

During the firm's second conference call to date, Séguin said that the firm's 21 Fr second-generation and 18 Fr third-generation delivery catheters have given CoreValve increased confidence in its business.

The firm is conducting a multi-center study of the 21 Fr device and plans to seek CE mark for the 18 Fr version in the second half of 2007.

The catheters deliver the firm's self-expanding multi-level frame, which holds the porcine pericardium tissue valve. Feasibility studies could begin in the U.S. in late 2006, with U.S. approval anticipated in 2010.

Thus far, the French start-up has raised $8 mil. in seed money and $24 mil. through a Series B financing led by Sofinnova, Apax Partners and Healthcap.

Given the current burn rate and plans to double staff from 15 to 30 employees during 2006, funds are likely to dry up by the end of 2007, "at which point we expect to be on the verge of commercialization in Europe and initiating our clinical trials in the U.S.," he noted.

In the U.S., CoreValve is pursuing approval of ReValving for use in high-risk patients and is competing with Edwards (***PVT***) to be first to market.

Edwards suspended its U.S. feasibility trial in June after finding that its "antegrade" approach for the PVT percutaneous aortic valve was less successful than an approach that passes the valve on a catheter through the femoral vein, across the mitral valve and into the aortic valve. The firm plans to begin enrolling patients by year-end for a new study that uses the new approach ([1]"The Gray Sheet" June 20, 2005, p. 17).

EXHIBIT 7

A Product, News and Clinical Update for the Cardiac Catheterization Laboratory Specialist

Cath Lab Digest

Feature:
Percutaneous Aortic Valve Replacement with a Self-Expanding Stent: The CoreValve ReValving™ Procedure

- Cath Lab Digest talks with founder Dr. Jacques R. Sequin about inserting a heart valve prosthesis in the cath lab

How did the percutaneous ReValving™ System first come about? I am a former professor of heart surgery at Paris University. For 20 years, I did open heart surgeries for coronary bypasses and valve replacements. I figured out during valve replacement surgery that this procedure could be done without having to open the chest or the heart. I thought it should not be necessary for valve replacement patients, especially the elderly ones, to have to endure two months of recovery and another six months before returning to their normal lives.

As a result, in 1999, I began developing what is now the ReValving™ system stent. After developing the initial steps of this concept, I decided to stop surgery and devote all my time to CoreValve, because I knew that if we could achieve a successful percutaneous procedure, we could change the face of how patients were treated. I felt myself to be more useful in developing this system than operating on patients everyday.

Can you describe the design of the device and its various components?

When I started all this, I knew definitely that surgeons would not be using the device, considering surgeons are unlikely to adopt noninvasive procedures. I tried to develop a device that the interventional cardiologist could use easily, a technique close to what they were using every day, but also, on the other hand, starting from a surgical point of view in regards to the characteristics of the implantation — in other words, trying to mimic what I was doing every day. I knew very well that the clinical essence of the device would be both the stent and what we put in the stent, the new valve. Once the stent is applied correctly, then what is left is the valve in the vascular flow, which is left for the whole life of the patient. We came up with the design as a result of the basic concept of homograft implantation. I developed the frame that hosts the tissue valve as a three-layer (or three-story) structure:

a) The lower part applies itself on the aortic annulus and has a high radial force. It can mimic the shape of the annulus, whether it is oval, circular or irregular. This is very important to assure the absence of para-valvular leaks around the newly implanted prosthesis.
b) The middle part, which is constrained to a given size, carries the new valve. As we all know, a tissue valve is designed with a specific size diameter that cannot be altered, so the middle portion of the stent has a very precise and stable diameter. Finally, the upper

Peripheral Venous Disease
Cardiac Arrhythmia
Aneurysm

stent area was given its concave shape to oppose the convex shape of the coronary sinus and the coronaries.
c) This higher part of the stent, which ends in the ascending aorta, has two additional functions. It helps to increase the fixation of the whole system and it serves to properly orient the prosthesis parallel to the flow.

The next step consisted of developing the percutaneous delivery system that would permit the implantation under standard cath lab conditions.

How do you implant the valve?
What we tried to do is to develop a technology that was as simple as possible, straightforward, and easily adaptable by the cardiologist without extensive training.

The first-generation ReValving device requires a surgical cut down on one of the inferior limb arteries. Then, after placing an extra stiff guidewire into the left ventricle, the delivery system is pushed over the wire and is positioned in the aortic annulus. Then progressively, the outer catheter wall is pulled back, and the valved frame auto-expands and pushes the native valve aside while anchoring in place. If the valve is heavily calcified, a single predilatation is recommended. The heart valve prosthesis is inventoried in its open shape, as with a standard tissue valve. Prior to delivery, it needs to be compressed onto the catheter. The nitinol is temperature-sensitive, and when you cool it down, it becomes soft and compressible. It is in this state that it can be loaded onto the delivery system.

The most important factor of our frame is that it is self-expanding. We chose self-expanding for a number of reasons. First, if we had used a balloon-expandable stent, we would have to balloon inside the flow, and therefore interrupt blood flow to the brain for the time of expansion. Secondly, when the balloon is inflated, it would compress the tissue valve against the metallic frame, creating some degree of trauma to the valve tissue and possibly decreasing its durability. The third issue is that a self-expanding stent can adapt itself to any shape of annulus, and this considerably reduces the possibility of para-valvular leaks, which have been a problem with other devices. Finally, once you have implanted a self-expanding stent, there is substantial residual radial force pushing on the tissue, assuring not only proper seating but also compression of the calcified part of the native valve. It is important to keep in mind that a balloon-expandable stent would not offer this advantage because it does recoil to a certain degree, which is unfavorable in front of calcified tissue.

Once implanted, how stable and durable is the valve?
The radial force of the stent is sufficient in ensuring a solid and stable anchoring of the new prosthesis. During the course of experimentation on more than 80 animals, no migration was ever noted. Cadaver studies reinforced our belief that the anchoring is absolute. The limited clinical data that we have from the feasibility study also shows no migration.

Before implanting our device in humans, we completed substantial durability testing, as you would do with any new valve. This work was performed by Professor Reul in Aachen, Germany. We also tested whether or not compressing this valve inside the frame for the duration of the delivery cycle would traumatize the valve. A testing protocol that compressed and decompressed the valve in a manner similar to the delivery manipulation showed no trauma to the valve leaflets by microscopy, scanning electron microscopy and

histology.

Can you explain what type of tissue is used for the valve?
The tissue used is of the same type, and undergoes the same preparation processes as the tissue from valves used for surgical implantation. There are many different tissue types in use today, but the predominant ones are mainly porcine valves or valves engineered from bovine pericardium. We are currently using bovine pericardium, because its thickness and flexibility characteristics allow for optimal mounting in our stent design. The tissue is sewn into the frame using the same surgical stitching techniques employed in the manufacture of standard surgical tissue valves.

Two patients have undergone the ReValving procedure.
Aortic valves can be either stenotic or regurgitant. If they are stenotic, the flow cannot exit the heart correctly. If they are regurgitant, once the flow has exited, it comes back into the heart. We were fortunate enough to be able to treat patients with the two different diseases during our first cases. The first patient had a highly stenotic calcified valve. We predilated the native valve and implanted our device without procedural complications. Post implantation, we observed good and immediate valve function without para-valvular leakage and with good gradients.
The second patient exhibited severe aortic valve regurgitation. No pre-dilatation was required and post implantation of our device, we again observed good and immediate valve function, without para-valvular leakage and with good gradients. It was very gratifying to see confirmation that we can treat the whole span of aortic valve disease.

What are your current plans in terms of doing further testing or trials?
We plan to conclude our feasibility trials in Asia. We will also initiate additional feasibility trials in Europe on high-risk patients. Actually, we received our first European IRB approval at Dr. Grube's center, the Heart Center Siegburg in Germany. During 2005, we will begin our pivotal trial in Europe to obtain CE marking. This trial will include all types of patients, contraindications to surgery as well as standard patients that would otherwise go to surgery. We will be treating both regurgitant valves and stenotic valves. In the meantime, we will be discussing the U.S. pivotal trial requirements with the FDA.

It should also be noted that this summer we opened a new facility in Irvine, California. The intent is to be totally independent in terms of having full control over all aspects of manufacturing all parts of our ReValving System.

Who are the physicians involved in working on the procedure?
We have a very distinguished scientific advisory board, comprised of both North American and European interventionalists. The U.S. and Canadian medical community is represented by Dr. Peter Block, Dr. Gregg Stone, Dr. Maurice Buchbinder and Dr. Raoul Bonan. From Europe, we have Patrick Serruys, Alec Vahanian, Jean-Claude Laborde and Eberhard Grube. Drs. Grube and Laborde were instrumental in our first two cases. Dr. Laborde from Toulouse, France performed all the animal implants, and has cooperated closely with the company in designing the system and achieving the result that we have today.

What do you feel is particularly unique about the ReValving system?
The most unique aspect is the self-expansion and the tri-level design of the CoreValve frame. Other aspects that differentiate us

from PVT (now owned by Edwards Lifesciences) include the fact that we are targeting all aortic valve patients and not just very high risk and compassionate cases. Finally, together with PVT/ Edwards, we are well ahead of other percutaneous aortic developmental programs which have not progressed beyond the concept or animal experimentation stage.

How do you treat patients post procedure?

The device is essentially a stent and a valve, not much different from surgically implanted tissue valves. So, following the implantation, we protect the patient and his/her new valve in the same way as post-surgical ones. A stent typically requires ticlopidine or Plavix in the short term and aspirin long term. A tissue valve typically needs coumadin for three months and then aspirin long term. Standard interventional protocols apply and the patient remains in the hospital overnight, to be discharged the next day.

How large is the catheter?

Any delivery system is always too large. The first-generation devices are 24 Fr. We are working hard on reducing the size to 20 Fr in the near future. As we get our device even smaller in future generational iterations, we are optimistic it will be technically possible to make it purely percutaneous, with its own closure system. At present, however, the current size does mean that when we implant the device, it is through a surgical cut down. We are creating a discipline that is medical-surgical or surgical-medical — the old war between surgeons and cardiologists has subsided and we are confident that the two specialties will cooperate in the best interest of the patient. We are definitely seeing procedures being done by both in the same room. Probably, in the future, there will be a new type of specialty physician that will able to perform hybrid surgical-interventional procedures.

How long does the procedure take?

From the moment you insert the catheter to the moment you retrieve the catheter is approximately 45 minutes. Deployment of the system itself takes about three to four minutes.

Following traditional surgery, the patient stays about 12–24 hours in the intensive care unit and four to five days in the hospital. It takes the patient about one month to recover and two

-IN THE NEWS: *Percutaneous Diagnosis of Aortic Valve Disease*

Vascular Solutions Announces 510(k) Clearance for Langston Dual Lumen Pigtail Catheter

Vascular Solutions, Inc. has received 510(k) clearance from the U.S. Food & Drug Administration for the Langston dual lumen pigtail catheter. The Langston catheter is a two-lumen diagnostic catheter indicated for use in the simultaneous measurement of pressures from two locations in the arterial system. Receipt of the 510(k) clearance will allow sales of the Langston catheter to commence in the U.S. through Vascular Solutions' direct sales force.

The patent pending design of the Langston catheter was developed by Mr. Phil Langston, Cath Lab Manager of Tulsa Regional Medical Center in Tulsa, Oklahoma. The design has been exclusively licensed to Vascular Solutions on a worldwide basis.

Howard Root, Chief Executive Officer of Vascular Solutions, noted, "The Langston catheter offers simultaneous accuracy and precise responsiveness in measuring intra-arterial pressure gradients, which is often used in diagnosing valvular disease. We estimate the Langston catheter is the only pigtail catheter available on the U.S. market today that can

months to go back to work, if they are relatively young. However, following the ReValving procedure, the patient requires only an overnight stay, and the overall procedural costs are likely to be half those incurred with traditional surgery.

be used to simultaneously measure differential intravascular pressures."

We have tried since the beginning design efforts to make things as simple as possible and as close to what the cardiologist is doing already: putting in a guidewire, pushing a delivery system, positioning the device, delivering the device and retrieving the access tools. ReValving training will be minimal. The biggest lab prep change will be that they need to rinse the tissue valve before they load it. Also, cardiologists need to acknowledge that they are now treating valves, and must treat the patient as a valve patient.

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EXHIBIT 8

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EXPEDITED REVIEW

Percutaneous Aortic Valve Replacement for Severe Aortic Stenosis in High-Risk Patients Using the Second- and Current Third-Generation Self-Expanding CoreValve Prosthesis

Device Success and 30-Day Clinical Outcome

Eberhard Grube, MD, FACC,* Gerhard Schuler, MD, FACC,† Lutz Buellesfeld, MD,* Ulrich Gerckens, MD,* Axel Linke, MD,† Peter Wenaweser, MD,* Barthel Sauren, MD,* Friedrich-Wilhelm Mohr, MD,† Thomas Walther, MD,† Bernfried Zickmann, MD,* Stein Iversen, MD,* Thomas Felderhoff, MD,* Raymond Cartier, MD,‡ Raoul Bonan, MD, FACC‡

Siegburg and Leipzig, Germany; and Montreal, Canada

Objectives We sought to determine both the procedural performance and safety of percutaneous implantation of the second (21-French [F])- and third (18-F)-generation CoreValve aortic valve prosthesis (CoreValve Inc., Irvine, California).

Background Percutaneous aortic valve replacement represents an emerging alternative therapy for high-risk and inoperable patients with severe symptomatic aortic valve stenosis.

Methods Patients with: 1) symptomatic, severe aortic valve stenosis (area <1 cm^2); 2) age ≥80 years with a logistic EuroSCORE ≥20% (21-F group) or age ≥75 years with a logistic EuroSCORE ≥15% (18-F group); or 3) age ≥65 years plus additional prespecified risk factors were included. Introduction of the 18-F device enabled the transition from a multidisciplinary approach involving general anesthesia, surgical cut-down, and cardiopulmonary bypass to a truly percutaneous approach under local anesthesia without hemodynamic support.

Results A total of 86 patients (21-F, n = 50; 18-F, n = 36) with a mean valve area of 0.66 ± 0.19 cm^2 (21-F) and 0.54 ± 0.15 cm^2 (18-F), a mean age of 81.3 ± 5.2 years (21-F) and 83.4 ± 6.7 years (18-F), and a mean logistic EuroSCORE of 23.4 ± 13.5% (21-F) and 19.1 ± 11.1% (18-F) were recruited. Acute device success was 88%. Successful device implantation resulted in a marked reduction of aortic transvalvular gradients (mean pre 43.7 mm Hg vs. post 9.0 mm Hg, $p < 0.001$) with aortic regurgitation grade remaining unchanged. Acute procedural success rate was 74% (21-F: 78%; 18-F: 69%). Procedural mortality was 6%. Overall 30-day mortality rate was 12%; the combined rate of death, stroke, and myocardial infarction was 22%.

Conclusions Treatment of severe aortic valve stenosis in high-risk patients with percutaneous implantation of the CoreValve prosthesis is feasible and associated with a lower mortality rate than predicted by risk algorithms. (J Am Coll Cardiol 2007;50:69–76) © 2007 by the American College of Cardiology Foundation

Cardiac valve diseases are considered as a major public health problem. A recent large population-based study revealed a steep increase of the prevalence of valvular heart diseases with age (1). In adults ≥75 years of age, aortic stenosis was present in as many as 4.6%. Of note, not only does symptomatic valvular heart disease become more prevalent with age but also comorbidities that increase the risk for an operative valve replacement. The latter is the current standard therapy for aortic stenosis, with an operative mortality of <5% for first-time isolated aortic valve replacements (2). However, several factors have been identified as independently predictive for an increased risk of periprocedural or postprocedural mortality (3). For example, in patients with reduced systolic left ventricular ejection fraction, the rate of mortality increases to 10% (4). Furthermore, advanced age and renal disease increase the operative

From *HELIOS Heart Center Siegburg, Siegburg, Germany; †Heart Center Leipzig, Leipzig, Germany; and ‡Institut de Cardiologie de Montreal, Montreal, Canada. Drs. Grube and Bonan are consultants to CoreValve.

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Abbreviations and Acronyms

AS = aortic stenosis
F = French
MACCE = major adverse cardiovascular and cerebral event
MI = myocardial infarction

mortality risk markedly (odds ratio 4.2) (4,5). The need for alternative treatment options for patients with severe aortic stenosis (AS), particularly in combination with comorbidities, is justified by the fact that as many as one-third of elderly comorbid patients with symptomatic AS were denied surgery in the EuroHeart survey (6). Especially for high-risk patients, the "gold standard" treatment with a conventional surgery may not be the best option. A less-invasive procedure to minimize cardiovascular complications associated with general anesthesia, thoracotomy, and heart-lung machine is required.

After the evaluation of a percutaneous valve replacement strategy in animal models (7–9), Cribier et al. (10) performed the first human implantation of a balloon-expandable aortic valve prosthesis with encouraging results. Nevertheless, the primarily used antegrade approach for valve implantation has shown to be very challenging (11). The innovation of a more flexible delivery catheter for the retrograde approach recently improved the procedural outcome (12). To avoid access site problems and to enhance stabilization during valve implantation, a transapical approach has been developed and is currently being tested (13,14).

An alternative technique with retrograde implantation of a self-expanding valve prosthesis (CoreValve prosthesis, CoreValve Inc., Irvine, California), which uses a porcine bioprosthesis within a nitinol frame, was first described in 2005 by our group (15). Subsequently, we have shown that the implantation procedure of the first- (24-French [F]) and second-generation (21-F) CoreValve device in 10 and 15 patients, respectively, is feasible and when successful results in marked hemodynamic and clinical improvements (16). Further device modifications have been realized since then and have reduced the sheath size from the initial 24-F to the present 18-F device (third-generation) (Figs. 1 and 2). In this report, we describe the procedural success and clinical outcome up to 30 days after implantation of the second- (21-F) and current third-generation (18-F) of the CoreValve revalving system.

Methods

Study design. A prospective multicenter, single-arm safety and performance study was performed that included the HELIOS Heart Center Siegburg, Germany, the Heart Center Leipzig, Germany, and the Institut de Cardiologie de Montreal, Canada. Our objective was to evaluate the feasibility, safety, and clinical outcome of implantation of the 21-F and 18-F self-expanding CoreValve aortic valve prosthesis in high-risk patients with aortic valve disease (stenosis with or without regurgitation) using a retrograde percutaneous transvascular approach. The study was approved by the local medical ethics committees, and all patients signed informed, written consent.

Patient population. A total of 86 consecutive patients were included in the present analysis. The study started in August 2005 with the 21-F device and enrolled a total of 50 patients (n = 25 in Siegburg, n = 14 in Leipzig, and n = 11 in Montreal). At the end of September 2006, the 18-F device became available and was later used exclusively for 36

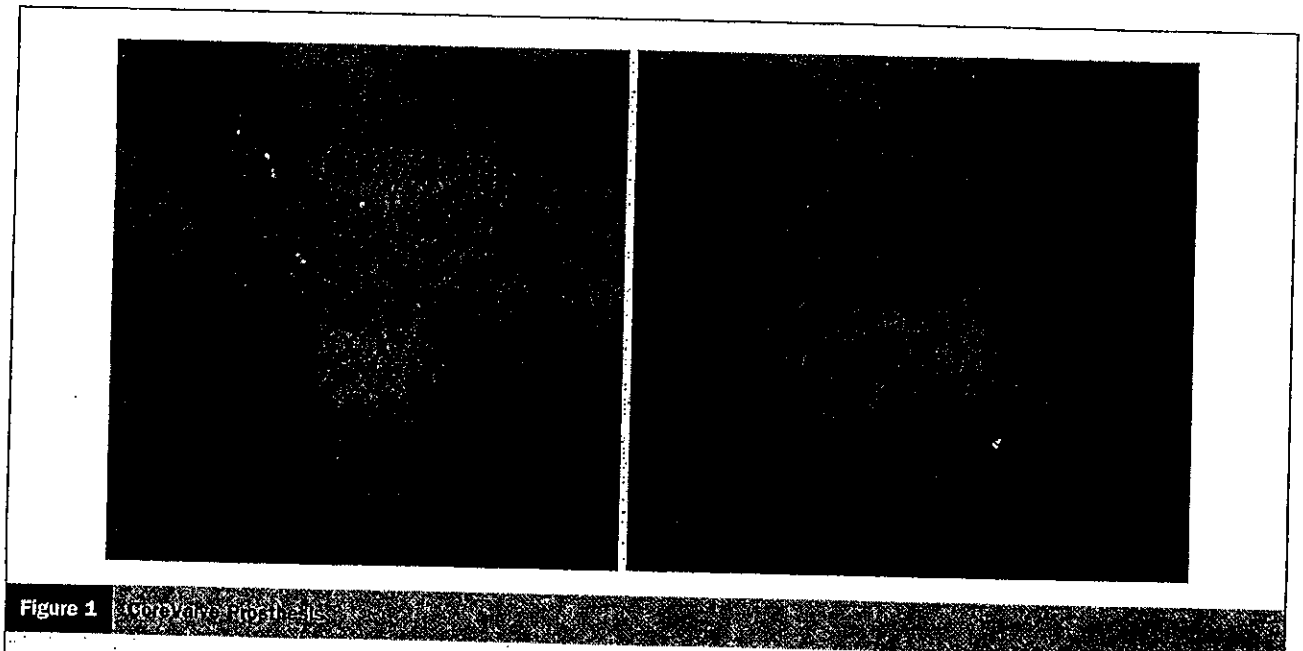

Figure 1 CoreValve Prosthesis

Third generation of the CoreValve prosthesis (18-F) before loading into the delivery catheter.

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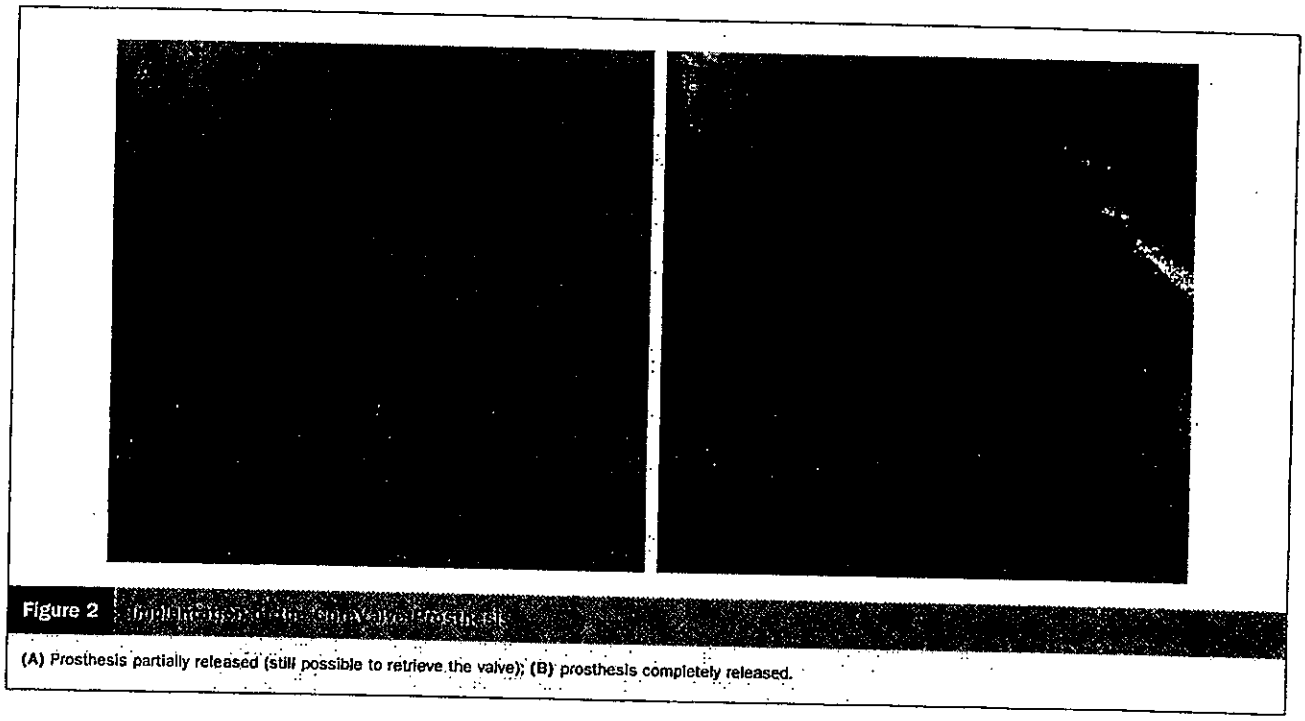

Figure 2 Implantation of the CoreValve Prosthesis

(A) Prosthesis partially released (still possible to retrieve the valve); (B) prosthesis completely released.

patients until February 2007 (n = 18 in Siegburg, n = 10 in Leipzig, and n = 8 in Montreal).

Inclusion criteria were the following: 1) severe native aortic valve stenosis with an area <1 cm^2 or <0.6 cm^2/m^2, with or without aortic valve regurgitation and age $\geq$80 years or a logistic EuroSCORE of $\geq$20% for the 21-F group and age $\geq$75 years or logistic EuroSCORE $\geq$15% for the 18-F group, respectively, or age $\geq$65 years and at least one of the following complications: cirrhosis of liver, pulmonary insufficiency (forced expiratory volume in one second <1 l), previous cardiac surgery, pulmonary hypertension >60 mm Hg, porcelain aorta, recurrent pulmonary embolus, right ventricular insufficiency, thoracic burning sequelae with contraindication for open chest surgery, history of mediastinum radiotherapy, severe connective tissue disease with contraindication for surgery, or cachexia (body mass index $\leq$18 kg/m^2). 2) Echocardiographic aortic valve annulus diameter $\geq$20 and $\leq$27 mm. 3) Diameter of the ascending aorta $\leq$45 mm at the sinotubular junction.

Exclusion criteria included hypersensitivity or contraindication to any study medication; sepsis or active endocarditis; excessive femoral, iliac or aortic atherosclerosis, calcification, or tortuosity; aortic aneurysm; bleeding diathesis or coagulopathy; recent myocardial infarction or cerebrovascular accident; mitral or tricuspid valvular insufficiency ($>$ grade II); left ventricular or atrial thrombus; uncontrolled atrial fibrillation; previous aortic valve replacement; polyarterial patients with either severe iliac or aortic vascular condition that make an insertion impossible or symptomatic carotid or vertebral arteries narrowing ($>$70%) disease or abdominal/thoracic aortic aneurysm; progressive disease with life expectancy <1 year; pregnancy; or creatinine clearance <20 ml/min.

Preinterventional morphological patient screening included transthoracic as well as transesophageal echocardiography, carotid and arteriovenous duplex ultrasonography, computed tomographic angiography, optional cardiac magnetic resonance imaging, and invasive cardiac evaluation with coronary angiogram and left ventriculography. The baseline operative risk of the patients was estimated by the logistic EuroSCORE (18). The patient was considered high risk if there was a consensus among an independent cardiologist and cardiac surgeon that conventional surgery would be associated with excessive morbidity and mortality.

Device description and procedure. The CoreValve aortic valve prosthesis consists of a trileaflet bioprosthetic porcine pericardial tissue valve, which is mounted and sutured in a self-expanding nitinol stent (Fig. 1). The prosthetic frame (stent) is manufactured by laser cutting and has an overall length of 50 mm. Further details of the device have been described previously (17). The second-generation (21-F) and third-generation (18-F) (Fig. 1) devices were used in the present study.

Vascular access was obtained either with or without standard surgical cutdown of the common iliac artery, the common femoral artery, or the subclavian artery. The procedure was performed with the patient under general anesthesia or with just local anesthesia in combination with a mild systemic sedative/analgesic treatment. The use of transesophageal echocardiographic guidance and the type of hemodynamic support (extracorporeal percutaneous femorofemoral bypass, tandem heart, extracorporeal membrane oxygenation, or none) was left to the discretion of the

operator. Balloon valvuloplasty with a 20- to 23-mm balloon under rapid pacing was performed before device placement, after which over a stiff guidewire, placed in the left ventricle, the device was deployed retrogradely under fluoroscopic guidance. If used, extracorporal circulatory support was activated just before device placement across the native valve position and terminated immediately after withdrawal of the delivery catheter and confirmation of adequate valve function. Hemodynamic and echocardiographic outcomes were assessed serially during the procedure. Evaluation of postprocedural regurgitations was performed using a supra-aortic angiogram and echo. After the procedure, the patients were transferred to the intensive care unit.

Clinical follow-up and transthoracic echocardiography were performed postprocedure, at hospital discharge, and 30 days after device implantation. Additional clinical and echocardiographic follow-up is planned on a yearly basis for at least 4 years after the implantation.

Antiplatelet and antithrombotic medication. Acetylsalicylic acid (100 mg/day) was administered before the procedure and continued indefinitely. In addition, all patients received clopidogrel (300-mg loading dose), followed by 75 mg daily for at least 6 to 12 months. During the intervention, the patient received weight-adjusted intravenous heparin to achieve an activated clotting time of 300 to 350 s for the duration of the procedure.

Definitions and statistical analysis. Clinical adverse events were adjudicated by an independent clinical events committee. Device success was defined as stable device placement and adequate function as assessed by angiography and echocardiography. Acute procedural success was defined as device success with absence of periprocedural major adverse cardiovascular and cerebral events (MACCEs) in the first 48 h after device implantation. Major adverse cardiovascular and cerebral events consisted of death from any cause, myocardial infarction (creatine kinase-myocardial band >2 × the upper limit of normal), cardiac tamponade, stroke (as assessed by routine neurological assessment before and after procedure and before hospital discharge), urgent or emergent conversion to surgery or balloon valvuloplasty, emergent percutaneous coronary intervention, cardiogenic shock, endocarditis or aortic dissection. Major bleeding was defined as hemorrhage requiring surgery and/or 3 or more units of blood transfusion.

Categorical variables are presented as frequencies and were compared by chi-square test. Continuous variables are presented as mean ± standard deviation. A 2-tailed unpaired Student *t* test for comparison between groups and a paired Student t test for intragroup comparison was used. A p value of <0.05 was considered statistically significant.

Results

Patient population. Between August 2005 and February 2007, 86 symptomatic patients (30 men and 56 women) with a mean age of 82 years, were included in the study. A total of 50 patients were enrolled for the 21-F and 36 patients for the 18-F device, respectively. Baseline patient characteristics are given in Table 1.

All patients had severe symptomatic AS with a mean transvalvular gradient of 43.7 ± 15.4 mm Hg and peak transvalvular aortic pressure gradient of 70.9 ± 22.8 mm Hg. The preprocedural mean calculated aortic valve area was 0.60 ± 0.16 cm^2 (range 0.3 to 1.0 cm^2) and the systolic left ventricular ejection fraction 54.1 ± 16.3% (range 19% to 80%). In 18 patients, a mild-to-moderate aortic regurgitation was present (n = 16 with grade 2+, n = 2 with grade 3+, respectively) whereas 68 patients presented with a grade 1+ (n = 48) or no aortic (n = 20) regurgitation. The mean calculated logistic EuroSCORE of the study population was 21.7 ± 12.6% and 83% of patients were New York Heart Association functional class III or IV.

Acute procedural and clinical results. Acute device success was achieved in 76 (88%) of 86 enrolled patients (Table 2) with no difference between the 2 groups (88% vs. 89%, p = NS) (Table 2). In 6 patients, misplacement of the valve led to urgent conversion to operative valve replacement (Table 2). In 2 patients, the device did not cross the heavily calcified native valve despite a balloon predilatation and, therefore, only a balloon valvuloplasty was performed. In 2 patients, a suboptimal placement of the prosthesis with remaining aortic

Table 1

	Overall (n = 86)	21-F (n = 50)	18-F (n = 36)
Female gender, n (%)	56 (65)	33 (66)	23 (64)
Diabetes mellitus, n (%)	27 (31)	18 (36)	9 (25)
Coronary artery disease, n (%)	48 (56)	24 (48)	24 (67)
Prior myocardial infarction, n (%)	11 (13)	7 (14)	4 (11)
Prior bypass graft surgery, n (%)	16 (19)	10 (20)	6 (17)
Prior valvuloplasty, n (%)	2 (3)	1 (2)	1 (3)
Left ventricular ejection fraction, % (mean)	54 ± 16	52 ± 18	57 ± 14
Peak pressure gradient, mm Hg (mean ± SD)	70.9 ± 22.8	66.0 ± 18.8	78.3 ± 26.0*
Aortic valve area, cm^2 (mean ± SD)	0.60 ± 0.16	0.66 ± 0.19	0.54 ± 0.15‡

*p = 0.003, †p = 0.016, ‡p = 0.003 for 21-F versus 18-F; all other p = NS.
NYHA = New York Heart Association.

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Table 2 Procedural Data

	Overall (n = 86)	21-F (n = 50)	18-F (n = 36)
Acute device success, n (%)			
Conversion to surgery, n (%)			
Only valvuloplasty, n (%)			
Valve-in-valve placement, n (%)			
Valvuloplasty after valve implantation,* n (%)	21 (24)	7 (14)	14 (39)
Procedural time, min (mean ± SD)			

*p = 0.009, based on 76 patients with successful valve implantation. †p = 0.002 for 21-F versus 18-F; all other p = NS.

regurgitation had to be corrected by implantation of a second CoreValve prosthesis (prosthesis-in-prosthesis).

The overall procedural success rate, that includes all MACCE within 48 h (26%) after implantation was 74% (78% for 21-F and 69% for 18-F, p = NS) (Table 3). The overall procedural MACCE rate excluding patients with conversion to valvuloplasty or surgery was 18%. Five deaths occurred periprocedurally: 2 patients died after conversion to balloon valvuloplasty (n = 1) and surgical aortic valve replacement (n = 1), respectively; 3 patients died of pericardial tamponade. The combined procedural rate of death, stroke, and myocardial infarction was 14%.

Overall, cardiac tamponades were observed in a total of 9 patients: 6 of them most likely were caused by wire perforations of the ventricle and treated either with pericardial puncture or surgical pericardiotomy. Two cases of tamponade occurred in the postoperative phase after urgent conversion to operative valve replacement, and one case of tamponade occurred in the postprocedural phase after pacemaker implantation. Neither an aortic dissection nor procedural coronary flow impairment was observed in the entire study population.

Table 3 Procedural Results (Periprocedural)

	Overall (n = 86)	21-F (n = 50)	18-F (n = 36)
Death, n (%)			
Stroke, n (%)	9 (10)	5 (10)	4 (11)
Major, n (%)	3 (4)	2 (4)	1 (3)
Minor, n (%)	6 (7)	3 (6)	3 (8)
Myocardial infarction, n (%)			
Cardiac tamponade			
Procedure related	6 (7)	1 (2)	5 (14)
After conversion to surgery	2 (2)	2 (4)	0
Aortic dissection, n (%)			
Coronary flow impairment, n (%)	0	0	0
Conversion to surgery or valvuloplasty, n (%)			
Procedural MACCE, n (%)	22 (26)	11 (22)	11 (28)
Procedural MACCE excluding conversion,† n (%)			
Combined death, stroke, MI, n (%)	14 (17)	7 (14)	7 (19)
Procedural success, n (%)			

*Includes MACCE within 48 h of valve implantation. †Based on 78 patients with device success, including valve-in-valve (n = 44 for 21-F; n = 34 for 18-F); no significant differences between groups.

MACCE = major adverse cardiac and cerebral events; MI = myocardial infarction; NYHA = New York Heart Association.

Table 4 Follow-Up Clinical Outcome

	Overall	21-F	18-F
Survival			
Death, n (%)			
Cardiovascular death, n (%)			
MI, n (%)			
Stroke, n (%)			
Combined death, stroke, MI, n (%)			
Survival			
In patients with acute device success	n = 76	n = 44	n = 32
Death, n (%)	7 (9)	3 (7)	4 (13)
Cardiovascular death, n (%)	6 (8)	3 (7)	3 (9)
MI, n (%)	1 (1)	1 (2)	0
Stroke, n (%)	7 (9)	4 (9)	3 (9)
Combined death, stroke, MI, n (%)	14 (18)	7 (16)	7 (22)
Survival			
Cardiovascular death, n (%)			
MI, n (%)			
Stroke, n (%)			
Combined death, stroke, MI, n (%)			

No significant differences between groups.
MI = myocardial infarction.

Follow-up clinical results. Overall mortality at 30 days was 12% in the intent-to-treat population with a combined rate of death, stroke and myocardial infarction of 22%. In patients with device and procedural success, the mortality was 9% and 5%, respectively (Table 4). With respect to the functional class, a remarkable relief of symptoms was observed with a decline from a mean New York Heart Association functional class of 2.85 ± 0.73 before to 1.85 ± 0.60 after valve implantation (p < 0.001).

Acute and follow-up echocardiographic results. The baseline echocardiographic measurements are given in Table 1. In case of a successful procedure, a striking improvement of hemodynamic parameters was observed in all patients, as illustrated in Figure 3 (example of a hemodynamic tracing at baseline and postimplantation) and Figure 4 (mean overall gradient pre vs. postvalve implantation). In 51 (66%) patients, the aortic regurgitation grade remained unchanged or was even reduced after the procedure. On the contrary, a worsening of the preinterventional aortic regurgitation grade after the procedure to grade 2+ was noted in 15 (20%) patients and from 0 to grade 1+ in 11 (14%). All of them were related to paravalvlar leakages as determined by echocardiography. Severe postprocedural aortic regurgitation (3+ or 4+) was not present in any patient. After 30 days, the overall grade of aortic regurgitation remained unchanged with a decrease of aortic regurgitation from grade 2+ to 1+ or 0 in 6 patients and an increase from grade 1+ to 2+ in 5 patients.

Comparison of procedural 21-F versus 18-F data. With the use of the smaller 18-F sheath significant improvements

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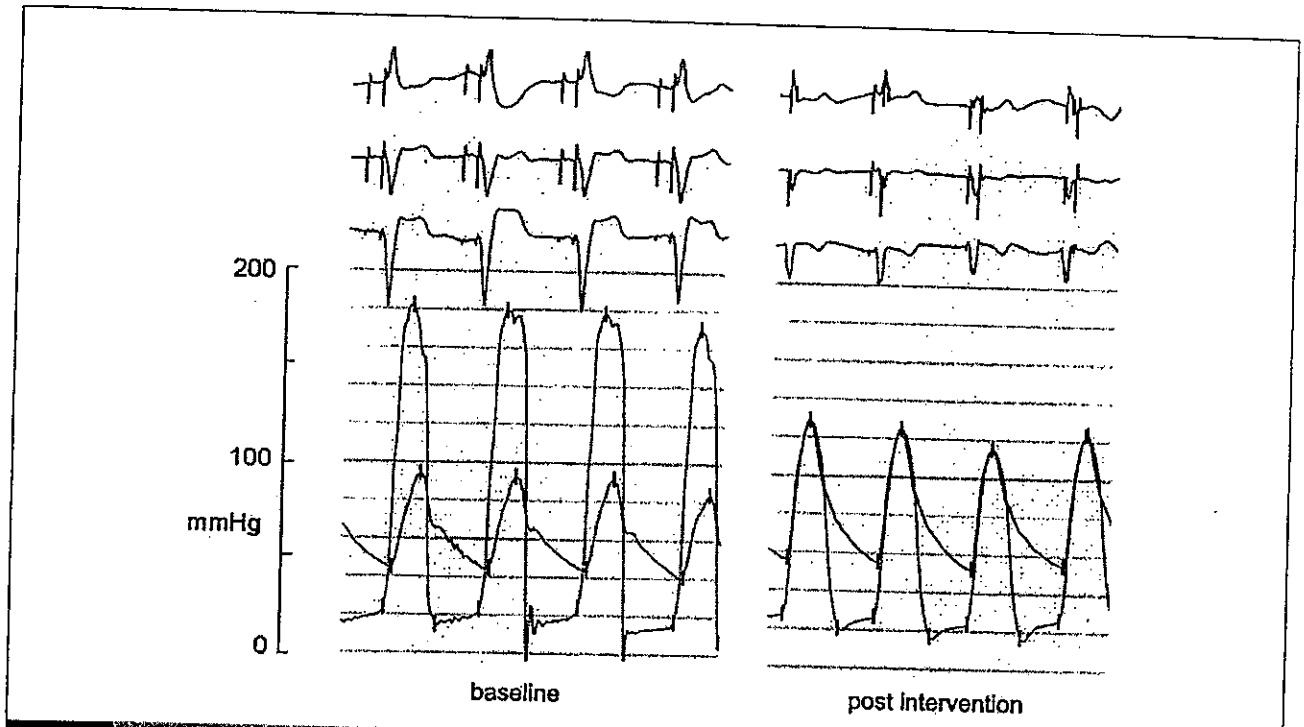

Figure 3 Hemodynamic Tracing Before and After CoreValve

Example of simultaneous left ventricular and aortic hemodynamic tracing at baseline and immediately after implantation of prosthesis.

with respect to procedural data were achieved: in the 18-F group, 25% of the procedures were performed only with local anesthesia of the groin (21-F group 0%, $p < 0.001$). Implantations without surgical cut-down for the access site vessel were significantly more frequently performed in the 18-F group (42%) than in the 21-F group (12%, $p = 0.001$). Moreover, 64% treated with the 18-F device had no hemodynamic support (0% with the 21-F device, $p < 0.001$), whereas for the 21-F group, a cardiac assist, extracorporeal membrane oxygenation or a full-bypass support always was applied. As a consequence, the total procedural time decreased markedly from 188 ± 55 min (21-F) to 148 ± 50 min (18-F, $p = 0.002$). A closure device (e.g., with Prostar device, Abbott Vascular, Abbott Park, Illinois) was used in all patients with percutaneous access.

Discussion

This research comprises the largest population treated with a percutaneous valve replacement system for treatment of degenerative, severe, symptomatic aortic stenosis. The analysis of this prospective multicenter study confirms the previously reported feasibility of the procedure (16) with a device success rate of 88% in these selected, high-risk patients. However, the fact that 8 patients of our population needed additional interventions by either second device implantation or conversion to surgery because of suboptimal implantation of the first prosthesis either too low or too high within the native valve area points out that accurate device deployment is crucial and certainly associated with a learning curve.

However, the CoreValve design provides several advantages that facilitate device deployment and reliable implantation: 1) a certain deployment error margin; 2) self-axing properties; 3) beneficial anchoring characteristics in native valve area as well as the ascending aorta; and 4) the ability for device retrieval after partial implantation of the first two-thirds of the prosthesis. This modified deployment technique, as opposed to the rapid complete deployment as favored in the beginning, has been introduced during the study course. Having deployed the distal two-thirds of the prosthesis (Fig. 2), the valve is already sufficiently functioning, whereas the device position can still be adjusted or the device can be pulled back completely.

The encouraging device success rate we have observed in this study goes along with a low procedural and 30-day mortality, which is lower than the predicted operative risk of these patients using the EuroScore risk algorithm (17). The accuracy and value of these risk assessment scores is sometimes controversially discussed. However, these tools are widely used for outcome stratification in high-risk surgical candidates in which large randomized clinical trails are missing. The population enrolled in our series presented with an average logistic EuroScore of 21.7%. The overall

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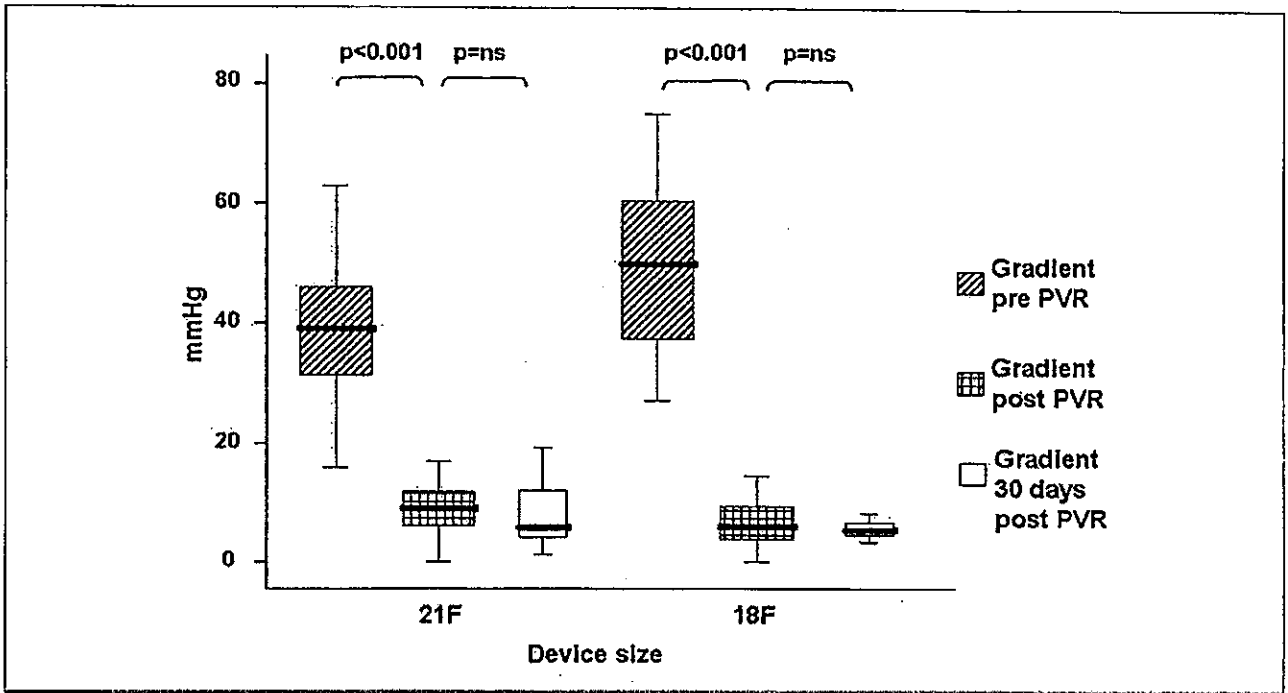

Figure 4

Mean gradient pre- versus postimplantation of prosthesis versus 30-day follow-up (for patients with procedural success). PVR = percutaneous valve replacement.

30-day mortality of 12% as well as the 30-day mortality of 9% in patients with acute device success in our study is therefore encouraging, proving the safety of the procedure with regard to this important clinical end point. In addition, if procedural success is achieved, the 30-day event rate is just 6%.

However, there was a relatively high rate of adverse events at 30 days in the overall intent-to-treat population, largely driven by cerebrovascular events and cardiac tamponades. The latter were induced in 6 cases, most likely by wire perforations during valve insertion and placement. Interestingly, most of these events occurred in the middle of the transition phase from the 21-F to 18-F period, when the less-invasive approach without hemodynamic support was introduced and a new device deployment technique was established. In this phase, it was realized that meticulous distal wire tip control is of particular importance for this procedure, given the characteristics of very stiff wires with a suboptimal tip shape for this procedural setting and their known potential for perforations.

Consequently, to address this issue, mandatory manual wire shaping is now performed before insertion, forming a less traumatic pigtail-like wire tip. In combination with continuous fluoroscopic tip position control, this measure reduced the incidence of wire perforations effectively in the later study phase. A specifically manufactured wire addressing these specific requirements would be certainly helpful to avoid the risk of perforations, a potentially life-threatening event which can occur in surgically treated patients in up to 17% (cardiac effusion) and 4% (tamponade) (18).

The problem of cerebrovascular events when treating patients with severe aortic stenosis is also already known from both the era of balloon valvuloplasty as well as surgical series. The risk of a perioperative cerebrovascular event for patients age ≥80 years of age undergoing coronary bypass surgery or combined bypass surgery and aortic valve replacement has been reported to be as high as 10% and 15%, respectively (3). Therefore, an overall stroke rate of 10%, including minor and major events in our study, is comparable with surgical data in this clinical setting. However, further progress is certainly needed to sufficiently prevent these embolic events during this kind of percutaneous approach. Whether these events are caused by thrombi or liberated plaque particles from the native valve, the ascending aorta or aortic arch, or air emboli is currently unclear. Careful device preparation to avoid air emboli, optimal device positioning without extensive placement maneuvers within the native valve, as well as adequate antiplatelet medication is certainly mandatory to reduce the incidence of embolic events.

The hemodynamic results of this study clearly demonstrate the efficacy of this new technique. As soon as the valve is adequately implanted, there is a striking reduction of the transvalvular gradient, usually without significant regurgitations. However, dilation afterward to fully expand the prosthesis, mainly in heavily calcific degenerated valves, is sometimes needed (24% in this study) to achieve a good hemodynamic outcome. However, this step can be performed safely and reliably, even with slightly oversized balloons, without risk for structural device damage. If

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regurgitation is still detected, it is usually located in the paravalvular area. We found that the acute postprocedural grade of regurgitation can still change in the following days, perhaps as the result of factors such as the self-expanding properties of the device (improvement) or a kind of recoil of the valve segment due to heavy calcifications (worsening). However, we have not observed any significant clinical worsening of regurgitation in the entire population. More long-term data are certainly needed to assess the durability of the acute hemodynamic results. The degeneration pattern of this pericardial valve is expected to be comparable with common aortic valve bioprostheses.

Although the CoreValve technique is still in its infancy, device modifications and procedural advances are proceeding. The device profile reduction to the 18-F catheter resulted in remarkable procedural improvements without different safety outcomes. The procedural duration is significantly reduced as the result of a less-invasive technique without need for ventricular assist devices, general anesthesia, and surgical access-site preparations. This third-generation device allows now a truly percutaneous approach to aortic valve replacement which has the potential to change the standards of care particularly for high-risk surgical candidates with severe AS in the near future.

Study limitations. The current multicenter study describes only the short-term results after CoreValve implantation; assessment of the long-term durability of this prosthesis will require at least a 5-year follow-up. There was no control group in this study, which limited our ability to assess the device efficacy. The results of this study apply only to the patient population enrolled (high-risk patients with aortic stenosis and multiple comorbid conditions). Additional studies are required to determine the suitability of this device for patients who are otherwise good candidates for surgical aortic valve replacement and those with predominant aortic regurgitation.

Conclusions

Percutaneous valve replacement with the CoreValve revalving system for selected patients with severe AS provides an encouraging device success rate, results in marked hemodynamic and clinical improvement, and is associated with a comparably low acute and 30-day mortality rate in this high-risk population. Further progress in terms of implantation technique, device positioning, as well as the device itself is warranted to reduce procedural-related adverse events.

Reprint requests and correspondence: Dr. Eberhard Grube, Department of Cardiology/Angiology, HELIOS Heart Center Siegburg, Ringstrasse 49, 53721 Siegburg, Germany. E-mail: GrubeE@aol.com.

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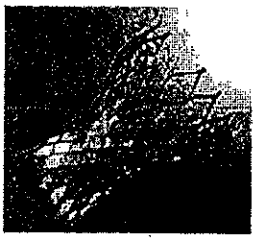
EXHIBIT 9

Posted date: 4/2/2007

Investors Back Pair of Heart Device Makers

HEALTHCARE: Money will go toward product tests, development

By Vita Reed
ORANGE COUNTY BUSINESS JOURNAL STAFF


Aortic Bioprosthesis

A couple of Orange County heart device makers landed more funding last week.

CoreValve Inc., which moved from France to Irvine last year, raised $33 million in a third round of venture funding. The latest round brings CoreValve's total to $63 million.

The other, Orqis Medical Inc., a Lake Forest heart device company, said it raised $12 million as part of its fourth round of venture capital. The funding brings Orqis' fourth-round total to $34.7 million. It raised $22.7 million in an earli funding round. Overall, Orqis has raised $73 million.

Maverick Capital Ltd. led CoreValve's investment. Existing investors that took part were Apax Partners, which has an office in Menlo Park, HealthCap, a Swedish venture fund, and Sofinnov Partners Inc., a French firm.

Orqis' funding saw three new investors lead the round: Salt Lake City-based Wasatch Advisors Inc. and its private equity affiliate, Cross Creek Capital LP, and the Omega Fund, which has a couple of offices, including one in London. Existing investors also participated, Orqis said.

CoreValve will use its latest funding to boost development of its heart valve and Percutaneous ReValving technique, which can be done on a beating heart via a catheter, cutting the need for open-heart surgery.

Orqis' products include Cancion, which is inserted through the skin to treat acute congestive heart failure, and Exeleras, an implantable pump that's used to treat patients with mid- to late-stage chronic heart failure.

The funding will allow Orqis to complete a pivotal clinical trial, submit a pre-market applicatio for Cancion to the Food and Drug Administration and get Exeleras through its first human trial, said Chief Executive Ken Charhut in a release.

Congestive heart failure is the breakdown of the heart's ability to pump blood through the body Some 5 million Americans have the disease and it's responsible for 4 million hospital visits a year, according to the American Heart Association.

CoreValve started off in Paris but moved its headquarters to Irvine with an eye toward raising money to fund Percutaneous ReValving's development.

"There is no doubt that we're going to need more money—it's a heart valve," said Rob Michiel CoreValve's chief operating officer and president, last year.

CoreValve actually opened an Irvine office in 1994, during a time that the company was workir on a catheter for delivering a valve to a patient's heart. The company's one of several in the fledgling market for heart valves that don't require major surgery.

Catheter-based replacement is expected to play a bigger part in heart surgery. Analysts and industry figures have estimated the market for such valves could reach $1 billion within 10 yea of approval.

The first catheter-based valves under development, however, aren't expected to be available un the end of the decade.

Three years ago, Irvine's Edwards Lifesciences Corp., the leader in conventional heart valves, paid $125 million for Percutaneous Valve Technologies Inc., a maker of catheter-inserted valve Other companies that are working on less-invasive products include Medtronic Inc., which has plant in Santa Ana, and Lake Forest-based 3F Therapeutics Inc., which now is part of Minnesota's ATS Medical Inc.

Both Charhut and Michiels have roots in what was then the heart unit of Baxter International Inc., which spun out as Edwards seven years ago.

Charhut spent 16 years in management positions in the unit, including a stint as president of Bentley Laboratories. Michiels held various global sales and marketing jobs with Edwards whe it was Baxter's cardiovascular business.

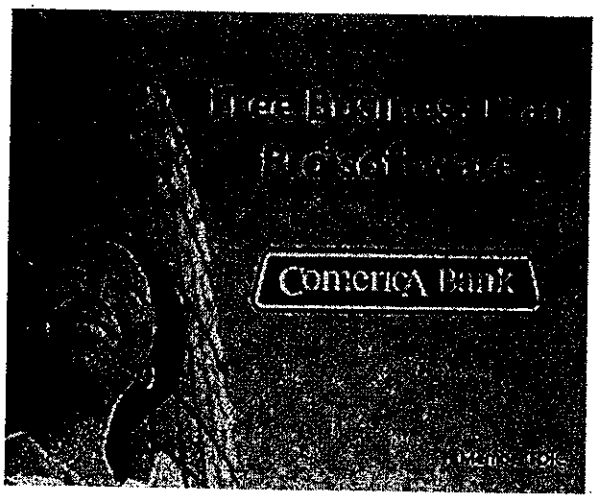


EXHIBIT 10

COREVALVE
THE REVALVING TECHNOLOGY

News Release

FOR IMMEDIATE RELEASE

Contact: Ronald Trahan, APR, Ronald Trahan Associates Inc., 508-359-4005, x108

CoreValve receives CE Mark approval for its *ReValving*™ System and announces plans to initiate expanded clinical evaluation

CoreValve's *ReValving*™ System is the first cath lab-based procedure for percutaneous aortic valve replacement to receive European regulatory clearance

IRVINE, Calif., May 16, 2007—CoreValve (www.corevalve.com) announced today that it has received CE Mark approval of its CoreValve Percutaneous ***ReValving***™ System for treatment of high-risk patients. The patented ***ReValving***™ System consists of a novel porcine pericardial tissue valve mounted in a self-expanding multi-level frame, which is permanently implanted over the diseased aortic heart valve by an **18-French**-sized catheter. The small size of the delivery catheter is a key element of the system as it greatly improves overall maneuverability and valve placement while also eliminating the need for surgical cut-down of the femoral artery.

CoreValve also announced that it will not immediately market the ***ReValving***™ System. Rather, the Company will proceed with an expanded clinical evaluation at a small number of select international centers to help ensure that interventional cardiologists are well trained, that patients are appropriately selected for treatment, and that appropriate clinical feedback is obtained. CoreValve has established a mandatory expanded clinical evaluation patient registry to gather additional clinical data for submission to the FDA in support of clinical trials and regulatory approval in the USA.

About CoreValve

Founded in 2001, privately held CoreValve—which is headquartered in Irvine, California—has developed a proprietary delivery system and tissue heart valve for percutaneous heart valve replacement. Based on a novel catheter-and-self-expanding-frame approach on a beating heart, the proprietary CoreValve ***ReValving***™ System procedure is intended to avoid open-heart surgery. It can be performed in a cardiac "cath lab" just like angioplasty and stenting, which may result in less trauma to the patient and may offer substantial cost-savings to the healthcare system. For more information about CoreValve, visit the Company's Web site at www.corevalve.com.

(Caution: the CoreValve ***ReValving***™ System will not be available in the USA for clinical trials or for commercialization until further notice.)

# # # # #

EXHIBIT 11

Andersen et al. U.S. Patent No. 5,411,552

Prosecuting Attorneys:

Richard H. Tushin
James M. Heslin

US005411552A

United States Patent [19]

Andersen et al.

[11] Patent Number: 5,411,552

[45] Date of Patent: May 2, 1995

[54] **VALVE PROTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTING SUCH VALVE PROTHESIS**

[76] Inventors: **Henning R. Andersen**, Dalvangen 37A, DK-8270 Hoejbjerg; **John M. Hasenkam**, Aprilvej 8, DK-8210 Aarhus V; **Lars L. Knudsen**, RudolfWulffsgade 6,4.mf., DK-8000 Aarhus C, all of Denmark

[21] Appl. No.: **261,235**

[22] Filed: **Jun. 14, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 961,891, Jan. 11, 1993, abandoned.

[30] **Foreign Application Priority Data**

May 18, 1990 [DK] Denmark 1246/90

[51] **Int. Cl.**[6] **A61F 2/24**

[52] **U.S. Cl.** 623/2; 623/900; 137/343; 137/844; 251/358

[58] **Field of Search** 623/2, 900; 137/343, 137/844, 316; 251/358; 606/108

[56] **References Cited**

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1371701	2/1988	U.S.S.R.	623/2

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Derwent Abstract No. 87-190867/27 (1987), SU 1271508 (Gorkii Kirov Medical Ins.).

Primary Examiner—David H. Willse
Attorney, Agent, or Firm—Watson, Cole, Grindle & Watson

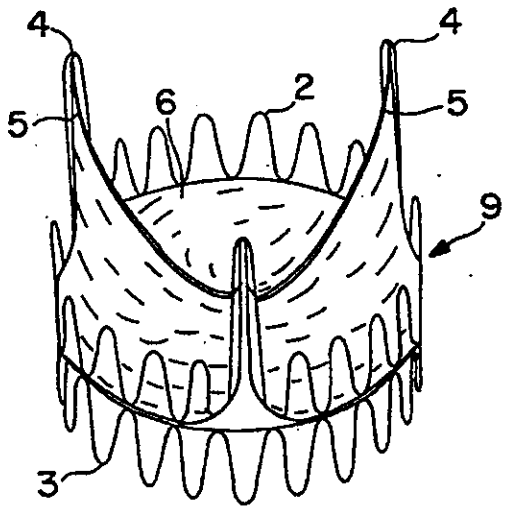
[57] **ABSTRACT**

A valve prosthesis (9) for implantation in the body by use of catheter (11) comprises a stent made from an expandable cylinder-shaped thread structure (2,3) comprising several spaced apices (4). The elastically collapsible valve (4) is mounted on the stent as the commissural points (5) of the valve (6) are secured to the projecting apices (4).

The valve prosthesis (9) can be compressed around the balloon means (13) of the balloon catheter (11) and be inserted in a channel, for instance in the aorta (10). When the valve prosthesis is placed correctly the balloon means (13) is inflated thereby expanding the stent and wedging it against the wall of aorta. The balloon means is provided with beads (14) to ensure a steady fastening of the valve prosthesis on the balloon means during insertion and expansion.

The valve prosthesis (9) and the balloon catheter (11) make it possible to insert a cardiac valve prosthesis without a surgical operation comprising opening the thoracic cavity.

8 Claims, 4 Drawing Sheets



SERIAL NUMBER (Series of 1987) 07/961891 | PATENT DATE | PATENT NUMBER

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
07/961,891	01/11/93	604	2	3306	WILLSE

APPLICANTS: HENNING R. ANDERSEN, HOEJBJERG, DENMARK; JOHN M. HASENKAM, AARHUS, DENMARK; LARS L. KNUDSEN, AARHUS, DENMARK.

CONTINUING DATA********
VERIFIED
Dn-nme

FOREIGN/PCT APPLICATIONS********
VERIFIED
Dn

PCT	PCT/DK91/00134	05/16/91	Dn 7-21-93
DENMARK	1246/90	05/18/90	Dn 7-21-93

***** SMALL ENTITY *****

Foreign priority claimed 35 USC 119 conditions met	Verified and Acknowledged	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
☒ yes ☐ no / ☐ yes ☐ no	Examiner's Initials	→	DKX	4	12	1	$655.00	66637-7

ADDRESS:
RICHARD H. TUSHIN
WATSON, COLE, GRINDLE & WATSON
1400 K STREET, N.W., SUITE 725
WASHINGTON, DC 20005

TITLE: ~~VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTATING SUCH VALVE PROSTHESIS~~
#6

U.S. DEPT. of COMM./Pat. & TM Office — PTO-436L (rev. 10-78)

PARTS OF APPLICATION FILED SEPARATELY

NOTICE OF ALLOWANCE MAILED	PREPARED FOR ISSUE		CLAIMS ALLOWED	
	Assistant Examiner	Docket Clerk	Total Claims	Print Claim

ISSUE FEE		DRAWING		
Amount Due	Date Paid	Sheets Drwg.	Figs. Drwg.	Print Fig.

Primary Examiner

Label Area

ISSUE CLASSIFICATION		ISSUE BATCH NUMBER
Class	Subclass	

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

Form PTO-436
Rev. 9/90

ATTORNEY'S DOCKET NUMBER

66637-7

3. A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
   c. ☒ has been transmitted by the International Bureau.
4. ☐ A translation of the International Application into English (35 U.S.C. 371 (c)(2)).
5. Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
6. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
7. ☒ An oath or declaration of the inventor (35 U.S.C. 371(c)(4)).
8. ☐ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36(35 U.S.C. 371(c)(5)).

Other document(s) or information included:

9. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
10. ☐ An assignment document for recording.
    Please mail the recorded assignment document to:
    a. ☐ the person whose signature, name & address appears at the bottom of this page.
    b. ☐ the following:

11. The above checked items are being transmitted
    a. ☐ before the 18th month publication.
    b. ☐ after publication and the Article 20 communication but before 20 months from the priority date.
    c. ☐ after 20 months but before 22 months (surcharge and/or processing fee included).
    d. ☐ after 22 months (surcharge and/or processing fee included).
       Note: Petition to revive (37 CFR 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 22 months *and no proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.*
    e. ☐ by 30 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
    f. ☒ after 30 months but before 32 months and a proper demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date (surcharge and/or processing fee included).
    g. ☐ after 32 months (surcharge and/or processing fee included).
       Note: Petition to revive (37 CFR 1.137(a) or (b)) is necessary if 35 U.S.C. 371 requirements submitted after 32 months and a proper demand for International Preliminary Examination was made by 19 months from the earliest claimed priority date.
12. At the time of transmittal, the time limit for amending claims under Article 19
    a. ☐ has expired and no amendments were made.
    b. ☐ has not yet expired.
13. ☐ Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____ (date), namely:
14. ☒ Other enclosures: Copy of WO 91/17720; Int. Exam. Rpt; retyped version of application with amended claims*

Richard H. Tushin, Esq.
NAME

Watson, Cole, Grindle & Watson
ADDRESS

1400 K Street, N.W., Suite 725

Washington, D.C. 20005

SIGNATURE

27,297
REGISTRATION NUMBER

Form PTO-1390 (Rev. 8-87) USCOMM-DC-97-3805

* To be used for examination!

PATENT

Attorney Docket No. 14635-007810
(Heartport Reference 001-F1)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

HENNING R. ANDERSEN et al.

Application No.: 08/261,235

Filed: June 14, 1994

For: VALVE FOR PROSTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTING SUCH VALVE PROSTHESIS

Examiner: WILLSE, D.

Art Unit: 3308

STATUS REQUEST LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please advise us of the status of this application.

Respectfully submitted,

James M. Heslin
Reg. No. 29,541

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
(415) 326-2400
Fax (415) 326-2422
JMH:lah

P:\DATA\PA2\PTO\DUMH\115401

Andersen et al. U.S. Patent No. 6,168,614

Prosecuting Attorneys:

James M. Heslin
Jens E. Hoekendijk

US006168614B1

(12) **United States Patent**
Andersen et al.

(10) **Patent No.: US 6,168,614 B1**
(45) **Date of Patent: *Jan. 2, 2001**

(54) **VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY**

(75) Inventors: **Henning Rud Andersen**, Hoejbjerg; **John Michael Hasenkam**; **Lars Lyhne Knudsen**, both of Aarhus, all of (DK)

(73) Assignee: **Heartport, Inc.**, Redwood City, CA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/026,574**

(22) Filed: **Feb. 20, 1998**

Related U.S. Application Data

(62) Continuation of application No. 08/955,228, filed on Oct. 21, 1997, now abandoned, which is a division of application No. 08/801,036, filed on Feb. 19, 1997, now Pat. No. 5,840,081, which is a continuation of application No. 08/352,127, filed on Dec. 1, 1994, now abandoned, which is a division of application No. 08/261,235, filed as application No. PCT/DK91/00134 on May 16, 1991.

(30) **Foreign Application Priority Data**

May 18, 1990 (DK) 1246-90

(51) **Int. Cl.**[7] **A61F 2/06**

(52) **U.S. Cl.** **623/1**; 623/2; 623/12; 623/900

(58) **Field of Search** 623/1, 2, 12, 11, 623/900

(56) **References Cited**

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(List continued on next page.)

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(List continued on next page.)

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"Valvular Heart Disease," Sixteenth Ed. of *The Merck Manual of Diagnosis and Therapy*, 1992, pp.546–553.

Primary Examiner—Jeffrey A. Smith
(74) *Attorney, Agent, or Firm*—Jens E. Hoekendijk; Michael J. Lynch

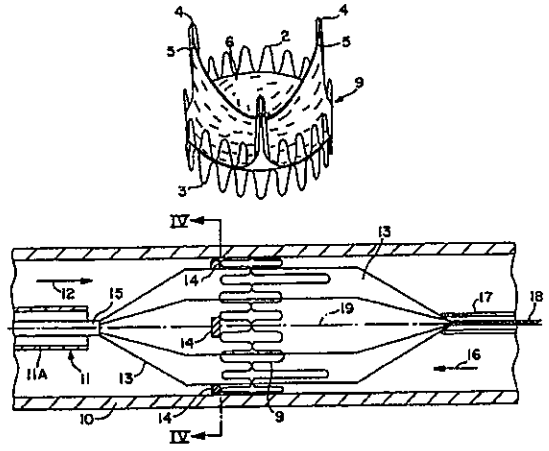
(57) **ABSTRACT**

A valve prosthesis (9) for implantation in the body by use of catheter (11) comprises a stent made from an expandable cylinder-shaped thread structure (2,3) comprising several spaced apices (4). The elastically collapsible valve (6) is mounted on the stent as the commissural points (5) of the valve (6) is secured to the projecting apices (4).

The valve prosthesis (9) can be compressed around the balloon means (13) of the balloon catheter (11) and be inserted in a channel, for instance in the aorta (10). When the valve prosthesis is placed correctly the balloon means (13) is inflated thereby expanding the stent and wedging it against the wall of the aorta. The balloon means is provided with beads (14) to ensure a steady fastening of the valve prosthesis on the balloon means during insertion and expansion.

The valve prosthesis (9) and the balloon catheter (11) make it possible to insert a cardiac valve prosthesis without a surgical operation comprising opening the thoracic cavity.

25 Claims, 4 Drawing Sheets



Bib Data Sheet

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/028,574	02/20/1998 RULE –	623	3732	001-D2-C1

APPLICANTS

HENNING RUD ANDERSEN, HOEJBJERG, ;
JOHN MICHAEL HASENKAM, AARHUS V, ;
LARS LYHNE KNUDSEN, AARHUS C, ;

** CONTINUING DATA **********

THIS APPLICATION IS A CON OF 08/955,228 10/21/1997 ABN
WHICH IS A DIV OF 08/601,038 02/19/1997 PAT 5,840,081
WHICH IS A CON OF 08/352,127 12/01/1994 ABN
WHICH IS A DIV OF 08/261,235 06/14/1994 PAT 5,411,552

** FOREIGN APPLICATIONS **********

DENMARK 1246-90 05/18/1990
UNITED STATES OF AMERICA PCT/DK91/00134 05/16/1991

** SMALL ENTITY **

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ yes ☐ no	–	4	28	2

35 USC 119 (a-d) conditions met: ☑ yes ☐ no ☐ Met after Allowance
Verified and Acknowledged: Examiner's Signature 3-7-00 Initials

ADDRESS

JAMES M. HESLIN
TOWSEND AND TOWSEND AND CREW LLP
TWO EMBARCADERO CENTER, 8TH FLOOR
SAN FRANCISCO, CA 941113834

TITLE

VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
483	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other ☐ Credit

HEARTPORT, INC.
200 Chesapeake Drive
Redwood City, CA 94063
(650) 306-7900

Heartport No. 007
Express Mail Label EM473459969US
Date of Deposit October 20, 1998

ASSISTANT COMMISSIONER FOR PATENTS
BOX PATENT APPLICATION
Washington, DC 20231

I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated below and is addressed to the Assistant Commissioner for Patents, Washington, DC 20231, Attn: Box Patent Application

By: Lori M. Cummings

Sir:

Transmitted herewith for filing under 37 CFR §1.53(b) is the continuation patent application of co-pending application Serial No. 08/955,228 filed October 21, 1997.

Inventor(s): HENNING R. ANDERSEN, J.M. HASENKAM and L.L. Knudsen

For: **A VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTING SUCH VALVE PROSTHESIS**

Application Elements:

[X] Specification (14 pages); 12 claims on pages 12-13.
[X] Four (4) sheets of formal drawings.
[X] Copy of Oath or Declaration from a prior application (37 CFR 1.63(d)) with Power of Attorney.
[X] Incorporation By Reference: the entire disclosure of the prior application, from which a copy of the Oath or Declaration is supplied is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
[X] A copy of Verified Statement Claiming Small Entity Status was filed in the prior application and is still proper and desired.
[X] Preliminary Amendment.

The filing fee has been calculated as shown below:

	NO. FILED		NO. EXTRA	SMALL ENTITY RATE	FEES
TOTAL CLAIMS	28-20 =	-	8	x11	$ 88
INDEP. CLAIMS	2-3 =	-	0	x41	$ —
BASIC FEE				$395	$395
				TOTAL	$483

Please charge Deposit Account No. 08-1510 the following fees:

[X] The filing fee of $395.00.
[X] The total cost of excess claims in the amount of $88.00
[X] Any additional fees or credit any overpayment to Deposit Account No. 08-1510 during the pendency of this application.
[X] 2 copies of this sheet are enclosed.

Respectfully submitted,

Jens E. Hoekendijk, Reg. No. 37,149
Attorney for Applicant

Telephone: (650) 306-7900
Facsimile: (650) 482-4287

Andersen et al. U.S. Patent No. 6,582,462

Prosecuting Attorneys:

Jens E. Hoekendijk
Mark D. Barrish
Emil Richard Skula
Brian S. Tomko
Thomas Spinelli

US006582462B1

(12) **United States Patent**
Andersen et al.

(10) **Patent No.: US 6,582,462 B1**
(45) **Date of Patent: *Jun. 24, 2003**

(54) **VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTING SUCH VALVE PROSTHESIS**

(75) Inventors: **Henning Rud Andersen**, Hoejbjerg (DK); **John Michael Hasenkam**, Aarhus V (DK); **Lars Lyhne Knudsen**, Aarhus C (DK)

(73) Assignee: **Heartport, Inc.**, Redwood City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/514,426**

(22) Filed: **Feb. 28, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/026,574, filed on Feb. 20, 1998, now Pat. No. 6,168,614, which is a continuation of application No. 08/955,228, filed on Oct. 21, 1997, now abandoned, which is a division of application No. 08/801,036, filed on Feb. 19, 1997, now Pat. No. 5,840,081, which is a continuation of application No. 08/569,314, filed on Dec. 8, 1995, now abandoned, which is a continuation of application No. 08/352,127, filed on Dec. 1, 1994, now abandoned, which is a division of application No. 08/261,235, filed on Jun. 14, 1994, now Pat. No. 5,411,552, which is a continuation of application No. 07/961,891, filed as application No. PCT/DK91/00134 on Mar. 16, 1991, now abandoned.

(30) **Foreign Application Priority Data**

May 18, 1990 (DK) 1246/90

(51) **Int. Cl.**[7] **A61F 2/24**
(52) **U.S. Cl.** **623/1.26**; 623/2.14
(58) **Field of Search** 623/FOR 101, 623/2.1–2.19, 2.38–2.41, 900, 904, 1.24–1.26

(56) **References Cited**

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World Medical Manufacturing Corp., Talent Endovascular Bifurcated Spring Graft System Composite Design brochure, no date.

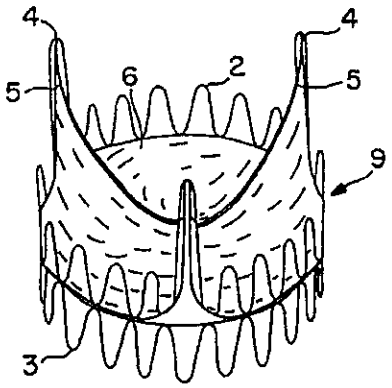
Derwent Abstract No. 87–1980867/27 (1987), SU 1271508 (Gorkii Kirov Medical Ins.).

Primary Examiner—David H. Willse

(57) **ABSTRACT**

A valve prosthesis for implantation in the body by use of a catheter includes a stent made from an expandable cylinder-shaped thread structure having several spaced apices. The elastically collapsible valve is mounted on the stent as the commissural points of the valve are secured to the projecting apices.

8 Claims, 4 Drawing Sheets



[redacted]
Bib Data Sheet

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/514,426	02/28/2000 RULE	623	3732	14635-007890US

APPLICANTS
Henning Rud Anderson, Hoejbjerg, DENMARK;
John Michael Hasenkam, Aarhus, DENMARK;
Lars Lyhne Knudsen, Aarhus, DENMARK;

** CONTINUING DATA **********
THIS APPLICATION IS A CON OF 09/026,574 02/20/1998 PAT 6,168,614
WHICH IS A CON OF 08/955,228 10/21/1997 ABN
WHICH IS A DIV OF 08/801,036 02/19/1997 PAT 5,840,081
WHICH IS A CON OF 08/352,427 12/01/1994 ABN
WHICH IS A DIV OF 08/261,235 06/14/1994 PAT 5,411,552
WHICH IS A 371 OF PCT/DK91/00134 05/16/1991

WHICH IS A CON OF 08/549,814 12/03/1995 ABN
WHICH IS A CON OF 07/951,841 01/4/1993 ABN

** FOREIGN APPLICATIONS **********
DENMARK 1246/90 05/18/1990
~~DENMARK 1246-90 05/18/1990~~

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** SMALL ENTITY **
** 04/19/2000

Foreign Priority claimed ☒ yes ☐ no 35 USC 119 (a-d) conditions met ☒ yes ☐ no ☐ Met after Allowance Verified and Acknowledged Examiner's Signature Initials	STATE OR COUNTRY DENMARK	SHEETS DRAWING 4	TOTAL CLAIMS 12	INDEPENDENT CLAIMS 1

ADDRESS
Jens E. Hoekendijk
Townsend and Townsend and Crew LLP
Two Embarcadero Center
8th Floor
San Francisco ,CA 94111-3834

TITLE
Valve prosthesis for implantation in the body and a catheter for implanting such valve prosthesis

FILING FEE RECEIVED 345	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other ☐ Credit

03-01-02

Customer No. 20350
TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
(415) 576-0200

ASSISTANT COMMISSIONER FOR PATENTS
BOX PATENT APPLICATION
Washington, D.C. 20231

Attorney Docket No. 14635-007890US
Client Ref No. 001-D2-C2
"Express Mail" Label No. EL515938319US
Date of Deposit: February 28, 2000

I hereby certify that this is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above, addressed to:

Assistant Commissioner for Patents
Washington, D.C. 20231

By: Stuart McLeish
STUART MCLEISH

Sir:

Transmitted herewith for filing under 37 CFR 1.53(b) is the
[ ] patent application of
[X] continuation patent application of
[ ] divisional patent application of
[ ] continuation-in-part patent application of

Inventor(s)/Applicant Identifier: HENNING R. ANDERSON, JOHN M. HASENKAM and LARS L. KNUDSEN

For: A VALVE PROSTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTING SUCH VALVE PROSTHESIS

[X] This application claims priority from each of the following Application Nos./filing dates: 09/026,574, filed 2/20/98; 08/955,228, filed 10/1/97; 08/801,035, filed 2/19/97; 08/569,314, filed 12/08/95; 08/352,127, filed 12/1/94; 08/261,235, filed 6/14/94 the disclosure(s) of which is (are) incorporated by reference.

Enclosed are:

[X] 14 page(s) of specification
[X] 2 page(s) of claims
[X] 1 page of Abstract
[X] 4 sheet(s) of formal drawing(s).
[X] The application is assigned of record to HEARTPORT, INC.
[X] A copy of the signed Declaration & Power of Attorney from the prior application.
[X] A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27 was filed in the prior application and small entity status is still proper and desired.
[X] Incorporation By Reference: the entire disclosure of the prior application, from which a copy of the Oath or Declaration is supplied is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
[X] A preliminary amendment.
[X] A copy of the notification of change of correspondence address filed in prior application.
[ ]
[ ]

FOR:	(Col. 1) NO. FILED	(Col. 2) NO. EXTRA
BASIC FEE		
TOTAL CLAIMS	12 - 20	= *0
INDEP. CLAIMS	2 - 3	= *0
[ ] MULTIPLE DEPENDENT CLAIM PRESENTED		

* If the difference in Col. 1 is less than 0, enter "0" in Col. 2.

SMALL ENTITY RATE	SMALL ENTITY FEE		OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
	$345.00	OR		$690.00
x $9.00 =	$0.00	OR	x $18.00 =	
x $39.00 =	$0.00	OR	x $78.00 =	
+ $130.00 =		OR	+ $260.00 =	
TOTAL	$345.00	OR	TOTAL	

Please charge Deposit Account No. 20-1430 as follows:
[X] Filing fee $ $345.00
[X] Any additional fees associated with this paper or during the pendency of this application.

[ ] A check for $_____ is enclosed.
2 copies of this sheet are enclosed.

Respectfully submitted,
TOWNSEND and TOWNSEND and CREW LLP

Mark D. Barrish
Reg No.: 36,443
Attorneys for Applicant

Telephone: (415) 576-0200
Facsimile: (415) 576-0300

PA 3053622 v1

CKET NO. HRT-10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DG
1-24-02

Applicants: Anderson et al.

Serial No.: 09/514,426 Art Unit: 3738

Filed : February 28, 2000 Examiner: D.Willse

For : A VALVE PROTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTING SUCH VALVE PROTHESIS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on

November 5, 2001
(Date of Deposit)

E. Richard Skula
(Name of applicant, assignee, or Registered Representative)

(Signature)

November 5, 2001
(Date of Signature)

RECEIVED
JAN 23 2002
TC 3700 MAIL ROOM

Commissioner For Patents
Washington, D.C. 20231

PETITION FOR EXTENSION OF TIME
AND AUTHORIZATION TO CHARGE
DEPOSIT ACCOUNT THEREFOR

Dear Sir:

Applicant(s) petition(s) the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated June 15, 2001 for two(2) month(s) from September 15, 2001 to November 15, 2001. An Amendment responding to the aforesaid Office Action is being filed concurrently herewith.

Please charge Deposit Account No. 10-0750/HRT010/ERS in the name of Johnson & Johnson for the cost of filing this Petition. Three copies of this Petition are enclosed.

Respectfully submitted,

01/17/2002 MGEBREM1 00000138 100750 09514426
01 FC:1116 400.00 CH

E. Richard Skula
Reg. No. 31,061
Attorney for Applicant(s)

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-2718
DATE: November 5, 2001

GP/3738/#

Docket No. HRT-0010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Anderson et al.

Serial No. : 09/514,426 Art Unit: 3738

Filed : February 28, 2000 Examiner: D. Willse

For : A Valve Prothesis for Implantation in the Body and a Catheter for Implanting Such Valve Prothesis

#16

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner For Patents, Washington, D.C. 20231 on

November 28, 2001
(Date of Deposit)

Brian S. Tomko
(Name of applicant, assignee, or Registered Representative)

(Signature)

November 28, 2001
(Date of Signature)

Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

Applicant(s) reserve(s) the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this

Please charge any deficiency or credit any overpayment to Deposit Account No. 10-0750/HRT-0010/BST. This form is submitted in triplicate.

Respectfully submitted,

Brian S. Tomko
Reg. No. 41349
Attorney for Applicants

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-1239
DATED: November 14, 2001

MATCH & RETURN

(4)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENTS

Applicant(s): Anderson et al.

Serial No: 09/514,426

Filed: February 28, 2000

For: A VALVE PROTHESIS FOR IMPLANTATION IN THE BODY AND A CATHETER FOR IMPLANTING SUCH VALVE PROSTHESIS

Examiner: D. Willse

Art Unit: 3738

Docket: HRT-10 (14966)

Dated:

Commissioner for Patents
United States Patent and Trademark Office
Washington, D.C. 20231

FAX RECEIVED
MAR 13 2003
GROUP 3700

AMENDMENT UNDER 37 CFR 1.312

Sir:

This amendment is filed to correct minor typographical errors in the claims.

CERTIFICATE OF FACSIMILE TRANSMISSION UNDER 37 C.F.R. §1.8(a)

I hereby certify that this correspondence is being facsimile transmitted to the Commissioner for Patents, Washington, D.C. 20231 at fax number 703-305-3591 on March 13, 2003.

Dated:

Elizabeth Handley

F:\WORK\1500\14966\AMEND\14966.AM2

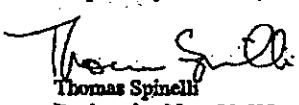
REMARKS

This amendment is being filed to correct minor typographical errors in the claims. No new matter is added.

Timely entry of this amendment is respectfully requested, particularly in view of the fact that a notice of allowability has been received.

If the Examiner believes that a telephone conference with Applicant's attorneys would be advantageous to the disposition of this case, the Examiner is requested to telephone the undersigned.

Respectfully submitted,



Thomas Spinelli
Registration No.: 39,533

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530

TS/rh

EXHIBIT 12

United States Patent and Trademark Office

Last Name	Tushin
First Name	Richard
Middle Name	H
Suffix	
Firm Name	Dykema Gossett PLLC
Address	1300 I Street NW Third Floor W
City	Washington
State/Province	DC
Postal Code	20005
Country	US
Primary Telephone	(202) 906-8680
Registration Number	27297
Attorney/Agent	ATTORNEY
Date Registered as Attorney	12/03/1974

Data extracted on Mon Apr 07 15:36:18 EDT 2008

United States Patent and Trademark Office

Last Name	Heslin
First Name	James
Middle Name	M
Suffix	
Firm Name	Townsend and Townsend and Crew LLP
Address	379 Lytton Ave
City	Palo Alto
State/Province	CA
Postal Code	94301
Country	US
Primary Telephone	(650) 326-2400
Registration Number	29541
Attorney/Agent	ATTORNEY
Date Registered as Attorney	12/28/1979

Data extracted on Mon Apr 07 15:35:10 EDT 2008

United States Patent and Trademark Office

Last Name	Hoekendijk
First Name	Jens
Middle Name	E
Suffix	
Firm Name	Hoekendijk and Lynch LLP
Address	601 Gateway Blvd Ste 780
City	South San Francisco
State/Province	CA
Postal Code	94080
Country	US
Primary Telephone	(415) 412-3322
Registration Number	37149
Attorney/Agent	ATTORNEY
Date Registered as Attorney	10/08/1993

Data extracted on Mon Apr 07 15:33:31 EDT 2008

United States Patent and Trademark Office

Last Name	Barrish
First Name	Mark
Middle Name	D
Suffix	
Firm Name	Townsend and Townsend and Crew
Address	379 Lytton Ave
City	Palo Alto
State/Province	CA
Postal Code	94301
Country	US
Primary Telephone	(650) 326-2400
Registration Number	36443
Attorney/Agent	ATTORNEY
Date Registered as Agent	04/19/1993
Date Registered as Attorney	02/22/1995

Data extracted on Mon Apr 07 15:40:26 EDT 2008

United States Patent and Trademark Office

Last Name	Skula
First Name	Emil
Middle Name	Richard
Suffix	
Firm Name	Johson & Johnson
Address	One Johnson & Johnson Plaza
City	New Brunswick
State/Province	NJ
Postal Code	08903
Country	US
Primary Telephone	(732) 524-2718
Registration Number	31061
Attorney/Agent	ATTORNEY
Date Registered as Attorney	06/27/1983

Data extracted on Mon Apr 07 15:41:52 EDT 2008

United States Patent and Trademark Office

Last Name	Tomko
First Name	Brian
Middle Name	S
Suffix	
Firm Name	Johnson & Johnson
Address	1 Johnson & Johnson Plaza
City	New Brunswick
State/Province	NJ
Postal Code	08933
Country	US
Primary Telephone	(732) 524-1239
Registration Number	41349
Attorney/Agent	ATTORNEY
Date Registered as Attorney	08/04/1997

Data extracted on Mon Apr 07 15:42:44 EDT 2008

United States Patent and Trademark Office

Last Name	Spinelli
First Name	Thomas
Middle Name	
Suffix	
Firm Name	Scully Scott Murphy and Presser
Address	400 Garden City Plaza
City	Garden City
State/Province	NY
Postal Code	11530
Country	US
Primary Telephone	(516) 742-4343
Registration Number	39533
Attorney/Agent	ATTORNEY
Date Registered as Agent	09/07/1995
Date Registered as Attorney	02/14/1996

Data extracted on Mon Apr 07 15:44:56 EDT 2008

EXHIBIT 13

Johnson & Johnson

OUR CARING TRANSFORMS

2007 Annual Report

PRINCIPAL OFFICE
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933
(732) 524-0400

ANNUAL MEETING
The Annual Meeting of Shareholders will take place April 24, 2008, at the Hyatt Regency New Brunswick, 2 Albany Street, New Brunswick, New Jersey. The meeting will convene at 10 a.m. All shareholders are cordially invited to attend. A formal Notice of Meeting, Proxy Statement and Proxy have been sent to shareholders.

CORPORATE GOVERNANCE
Copies of the Company's 2007 Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K to the Securities and Exchange Commission, Proxy Statement, and this Annual Report are available online at www.jnj.com, or to shareholders without charge upon written request to the Secretary at the Company's principal address or by calling (800) 328-9033 or (781) 575-2718 (outside the U.S.).

In addition, on the Company's Corporate Governance Web site at www.investor.jnj.com/governance, shareholders can see the Company's Principles of Corporate Governance, Charters of the Audit Committee, Compensation & Benefits Committee and Nominating & Corporate Governance Committee, Policy on Business Conduct for employees and Code of Business Conduct & Ethics for Members of the Board of Directors and Executive Officers. Copies of these documents are available to shareholders without charge upon written request to the Secretary at the Company's principal address.

The Company is required to file as an Exhibit to its Form 10-K for each fiscal year certifications under Section 302 of the Sarbanes-Oxley Act signed by the Chief Executive Officer and the Chief Financial Officer. In addition, the Company is required to submit a certification signed by the Chief Executive Officer to the New York Stock Exchange within 30 days following the Annual Meeting of Shareholders. Copies of the certifications filed for previous years are posted on the Company's Corporate Governance Web site, and future certifications will be posted promptly upon filing.

COMMON STOCK
Listed on New York Stock Exchange
Stock Symbol JNJ

SHAREHOLDER RELATIONS CONTACT
Steven M. Rosenberg
Corporate Secretary
(732) 524-2455

INVESTOR RELATIONS CONTACT
Louise Mehrotra
Vice President, Investor Relations
(800) 950-5089
(732) 524-6492

TRANSFER AGENT AND REGISTRAR
Questions regarding stock holdings, certificate replacement/transfer, dividends and address changes should be directed to:
Computershare Trust Company, N.A.
250 Royall Street
Canton, MA 02021
(800) 328-9033 or
(781) 575-2718 (outside the U.S.)
Internet: www.computershare.com

The paper used in this publication is made from 30% post-consumer recycled fiber, is Forest Stewardship Council™ certified for chain of custody and was manufactured with green energy credits for purchase of electricity generated from renewable-energy sources such as wind and low-impact hydro resources.

DIVIDEND REINVESTMENT PLAN
The Plan allows for full or partial dividend reinvestment, and additional monthly cash investments up to $50,000 per year, in Johnson & Johnson common stock without brokerage commissions or service charges on stock purchases. If you are interested in participating in the Plan and need an authorization form and/or more information, please call Computershare Trust Company, N.A. at (800) 328-9033 or (781) 575-2718 (outside the U.S.).

HEARING IMPAIRED
Shareholders who have inquiries regarding stock-related matters can communicate directly with Computershare Trust Company, N.A. via a telecommunications device (TDD). The telephone number for this service is (800) 952-9245 or (781) 575-2692 (outside the U.S.).

Registered shareholders who wish to receive electronic notice of online access to future annual reports and proxy materials instead of paper copies may register online at www.computershare.com/us/ecomms, or www.econsent.com/jnj for employees holding shares in one of the Johnson & Johnson savings plans.

WEB SITE
www.jnj.com

For more information on Johnson & Johnson history: www.kilmerhouse.com

For the Johnson & Johnson Web log: www.jnjbtw.com

EXHIBIT 14

Edwards Lifesciences Initiates Patent Infringement Litigation Against CoreValve

Infringement Suit Filed in Germany on Patent Relating to Transcatheter Heart Valve

IRVINE, Calif., May 10, 2007 -- Edwards Lifesciences Corporation (NYSE: EW), the world leader in the science of heart valves, announced today that its subsidiary, Edwards Lifesciences PVT, Inc., has filed a patent infringement lawsuit against CoreValve, Inc., of Irvine, Calif., in the District Court of Dusseldorf, Germany. The suit seeks relief for alleged infringement of a patent for transcatheter heart valve technology.

"We are committed to protecting our valuable intellectual property as well as the interests of our clinician-inventors who partner with us to transform patient care for people with advanced cardiovascular disease," said Michael A. Mussallem, Edwards' chairman and CEO. The Company has opened discussions with CoreValve on a possible licensing arrangement.

The relevant patent, EP 0 592 410 B1, is co-owned by Dr. Henning Rud Andersen of Aarhus, Denmark, and his colleagues, who licensed it in 1993 to Heartport, Inc., now a subsidiary of Johnson & Johnson. Edwards has an exclusive sublicense to the Andersen patent for cardiovascular applications. The patent relates to a valve prosthesis for implantation by means of a catheter, and the product named in the suit is the CoreValve ReValving System.

About Edwards Lifesciences

Edwards Lifesciences, a leader in advanced cardiovascular disease treatments, is the number-one heart valve company in the world and the global leader in acute hemodynamic monitoring. Headquartered in Irvine, Calif., Edwards focuses on specific cardiovascular disease states including heart valve disease, peripheral vascular disease and critical care technologies. The company's global brands, which are sold in approximately 100 countries, include Carpentier-Edwards, Cosgrove-Edwards, FloTrac, Fogarty, LifeStent, PERIMOUNT Magna and Swan-Ganz. Additional company information can be found at http://www.edwards.com.

###

Contact Information:
Media, Amanda C. Fowler, +1-949-250-5070, or Investors, David K. Erickson, +1-949-250-6826, both of Edwards Lifesciences Corporation

Edwards Lifesciences Initiates Patent Infringement Litigation Against CoreValve in the U.S.

IRVINE, Calif., Feb. 12, 2008 – Edwards Lifesciences Corporation (NYSE: EW), the world leader in the science of heart valves, announced today that it has filed a patent infringement lawsuit against CoreValve, Inc., of Irvine, Calif., in the United States District Court for the District of Delaware. The suit seeks injunctive relief and damages for infringement of three of the Andersen family of patents for transcatheter heart valve technology.

"Edwards has a significant portfolio of patents in transcatheter heart valve technology, led by the Andersen patent family, and we are committed to protecting this valuable intellectual property and the interests of our clinician-inventors," said Bruce P. Garren, Edwards' corporate vice president and general counsel.

In May 2007, Edwards initiated litigation against CoreValve in the District Court of Dusseldorf, Germany, for infringement of a related Andersen patent, EP 0 592 410 B1, and similar litigation is also now pending in the United Kingdom. The European litigations address the sale of CoreValve's infringing valves; the suit filed today is directed at CoreValve's manufacture of valves in the United States for export and sale in Europe.

The relevant U.S. patents, No. 5,411,552, No. 6,168,614 and No. 6,582,462 -- part of the Andersen patent portfolio -- are fully owned by Edwards. These patents relate to a valve prosthesis for implantation by means of a catheter, and the product named in the suit is the CoreValve ReValving System.

About Edwards Lifesciences

Edwards Lifesciences, a leader in advanced cardiovascular disease treatments, is the number-one heart valve company in the world and the global leader in acute hemodynamic monitoring. Headquartered in Irvine, Calif., Edwards focuses on specific cardiovascular disease states including heart valve disease, vascular disease and critical care technologies. The company's global brands, which are sold in approximately 100 countries, include Carpentier-Edwards, Cosgrove-Edwards, FloTrac, Fogarty, PERIMOUNT Magna and Swan-Ganz. Additional company information can be found at http://www.edwards.com.

###

Contact Information:
Media, Sarah Huoh, +1-949-250-5070, or Investors, David K. Erickson, +1-949-250-6826, both of Edwards Lifesciences Corporation

EXHIBIT 15

Seeking Alpha$^{\alpha}$

Edwards Lifesciences Corp. Q3 2007 Earnings Call Transcript

posted on: October 23, 2007 | about stocks: EW

Edwards Lifesciences Corp. (EW)
Q3 2007 Earnings Call
October 22, 2007, 05:00 PM

Executives

David K. Erickson - VP, IR
Michael A. Mussallem - Chairman and CEO
Thomas M. Abate - Corporate VP, CFO and Treasurer

Analysts

Paul Choi - Merrill Lynch
Larry Biegelsen - Wachovia Securities
Glenn Novarro - Banc of America Securities
Tim Nelson - Piper Jaffray
Glenn Reicin - Morgan Stanley
Chris Pasquale - J.P. Morgan Chase & Co.
Tim Lee - Caris & Company
Amit Bhalla - Citigroup
Alex Arrow - Lazard Capital Markets
Ashim Anand - Natexis Bleichroeder

Presentation

Operator

Greetings, ladies and gentlemen and welcome to the Edwards Lifesciences Third Quarter 2007 Earnings Conference Call. At this time, all participants are in a listen-only mode. A brief question-and-answer session will follow the formal presentation. [Operator Instructions]. As a reminder, this conference is being recorded.

It is now my pleasure to introduce your host, Mr. David Erickson, Vice President, Investor Relations. Thank you, Mr. Erickson; you may begin.

David K. Erickson - Vice President, Investor Relations

Welcome and thank you for joining us today. Just after the close of regular trading, we released our third quarter 2007 financial results. During our call today, we'll focus our prepared remarks on information that complements the material included in the press release and financial schedules, and then allocate the remaining time for Q&A.

Our presenters on today's call are Mike Mussallem, Chairman and CEO; and Tom Abate, CFO and Treasurer. Before I turn the call over to Mike, I'd like to remind you that during today's call, we will be making forward-looking statements that are based on estimates, assumptions and projections. These statements include, but aren't limited to sales, gross margin, net income, earnings per share, and free cash flow targets for 2007, the regulatory approval and sales of Heart Valve Therapy products including Magna mitral and Magna Ease, the competitive dynamics and market fundamentals

work with FDA to finalize the trial design. Although patient interest remains high, we now anticipate that enrollment in the PARTNER trial will be completed closer to the end of the 12 to 18-month timeframe that we initially projected. We continue to believe our progress in the U.S. gives us at least a two year lead over the next closest competitor.

As we announced last month, we received CE Mark to begin selling the SAPIEN valve in Europe with our RetroFlex transfemoral delivery system and we remain confident that we will receive the CE Mark for the Ascendra transapical delivery system by the end of the year.

As expected, we reached our goal of having 15 European reference centers trained by the end of the third quarter. Our European commercialization activities have begun and we are currently implementing a disciplined launch in training centers with available funding. Since receiving our CE Mark, we've seen an increase in the level of interest and enthusiasm for both cardiac surgeons and interventional cardiologist. We continue to expect to generate more than $20 million of transcatheter valve sales in 2008.

We continue to be pleased with our progress and the development of a next generation transcatheter heart valve with the reduced delivery profile, enhanced durability and unsurpassed hemodynamics. With our smaller delivery profile, we will make this technology available for an even wider group of patients. We anticipate the first clinical use of this new valve in the first half of 2008.

Recently, we also secured full ownership of the Andersen family of patents which relate to the transcatheter heart valve technology. Edwards previously had an exclusive license to these patents, they were acquired as part of the purchase of PVT in 2004. Last month, we entered into a transaction with Dr. Henning Andersen and his two co-inventors who assigned full ownership of the global Andersen patent portfolio to Edwards. We also acquired Johnson & Johnson's remaining license right to the Andersen patent which were obtained as part of the Heartport acquisition in 2001. These two transactions provide Edwards with greater overall control of the prosecution and enforcement of the Andersen patents in Europe and the U.S.

Turning to transcatheter mitral repair, you'll recall during the first quarter, we completed enrollment in the 60-patient EVOLUTION I feasibility study of our MONARC system for the treatment of functional mitral regurgitation. Yesterday, at TCT, Professor Alec Vahanian [ph] presented updated interim results from the study which demonstrated encouraging efficacy in the majority of patients in six months. Professor Vahanian also reported that the number of the patient experienced an undesirable compression of the coronary vessel, three of which resulted in clinically significant events. We'll be collecting and analyzing additional clinical data and have decided to postpone enrolment of EVOLUTION II until 2008 when that analysis is complete. We are continuing to pursue this technology and remain confident of patients with functional mitro-regurgitation represent a very large and attractive potential market with few treatment options.

As TCT continues, there will be additional clinical discussions and case presentations featuring our transcatheter technologies and peripheral vascular products. In addition, on Wednesday we will be hosting an analyst lunch featuring Dr. Gus Pichard who will share his clinical experience with our SAPIEN transcatheter valve and RetroFlex delivery system. And Dr. Alex Powell will discuss the one year results from our RESILIENT trial. For more information or to RSVP to this event, please contact our Investor Relations department.

Now I will turn the call over to Tom.

Thomas M. Abate - Corporate Vice President, Chief Financial Officer and Treasurer

Thank you, Mike. Reported Earnings per diluted share for the third quarter were $0.48 compared to $0.45 last year. Excluding special items, our third quarter 2007 non-GAAP EPS was $0.46 compared to $0.47 last year. Our gross profit margin for the third quarter was 65.3% compared to 64.7% in the same period last year. This 60 point basis point improvement was due to a more profitable profit mix and the positive impact from foreign exchange, partially offset by operating costs specific to the quarter.

For the fourth quarter, we expect the rate to improve, but fall below our prior guidance of 66%. Due to our hedging contracts, today's exchange rates have a slightly negative impact on our gross margin. For the full year 2007, we continue to expect an improvement between 100 to 150 basis points.

Third quarter SG&A expenses were $103 million or 39.5% of sales. This expected higher level of spending was due to additional investments for the SAPIEN valve launch in Europe, higher sales related spending in the U.S. and the impact from foreign exchange. For the fourth quarter, we expect SG&A as a percentage of sales to fall below 39%.

R&D investments in the quarter were $31 million or 11.8% of sales compared to $28 million last year. The increased level of spending was focused primarily on our transcatheter valve and Critical Care development efforts. For the fourth quarter, we expect R&D as a percentage of sales to remain at approximately 12%.

EXHIBIT 16

SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 12:30 PM 07/21/1999
991299896 - 3072398

CERTIFICATE OF INCORPORATION

OF

Percutaneous Valve Technologies Inc.

* * * * *

FIRST: The name of the corporation is Percutaneous Valve Technologies Inc. (hereinafter called the "Corporation").

SECOND: The address of its registered office in the State of Delaware is Corporation Trust Center, 1209 Orange Street in the City of Wilmington, County of New Castle. The name of its registered agent at such address is The Corporation Trust Company.

THIRD: The nature of the business and of the purposes to be conducted or promoted by the Corporation are to conduct any lawful business, to promote any lawful purpose, and to engage in any lawful act or activity for which corporations may be organized under the General Corporation Law of Delaware.

FOURTH: The total number of shares of stock which the Corporation shall have authority to issue is One Thousand (1,000) shares, all of which are of no par value each and all of which are of one class and are designated as Common Stock.

FIFTH: The name and mailing address of the sole incorporator is as follows:

NAME	MAILING ADDRESS
Erin L. Reilly	c/o 1209 Orange Street, Wilmington, DE 19801

SIXTH: The Corporation is to have perpetual existence.

SEVENTH: In furtherance and not in limitation of the powers conferred by statute, the board of directors is expressly authorized:

To make, alter or repeal the by-laws of the Corporation.

EIGHTH: Elections of directors need not be by written ballot unless the by-laws of the Corporation shall so provide.

Whenever a compromise or arrangement is proposed between this Corporation and its creditors or any class of them and/or between this Corporation and its stockholders or any class of them, any court of equitable jurisdiction within the State of Delaware may, on the application in a summary way of this Corporation or of any creditor or stockholder thereof or on the application of any receiver or receivers appointed for this Corporation under the provisions of Section 291 of Title 8 of the Delaware Code or on the application of trustees in dissolution or of any receiver or

receivers appointed for this Corporation under the provisions of Section 279 of Title 8 of the Delaware Code order a meeting of the creditors or class of creditors, and/or of the stockholders or class of stockholders of this Corporation, as the case may be, to be summoned in such manner as the said court directs. If a majority in number representing three-fourths in value of the creditors or class of creditors, and/or of the stockholders or class of stockholders of this Corporation, as the case may be, agree to any compromise or arrangement and to any reorganization of this Corporation as a consequence of such compromise or arrangement, the said compromise or arrangement and the said reorganization shall, if sanctioned by the court to which the said application has been made, be binding on all the creditors or class of creditors, and/or on all the stockholders or class of stockholders, of this Corporation, as the case may be, and also on this Corporation.

NINTH: The Corporation reserves the right to amend, alter, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by statute, and all rights conferred upon stockholders herein are granted subject to this reservation.

TENTH: A director of the Corporation shall not be personally liable to the Corporation or its stockholders for monetary damages for breach of fiduciary duty as a director except for liability (i) for any breach of the director's duty of loyalty to the Corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the Delaware General Corporation Law, or (iv) for any transaction from which the director derived any improper personal benefit.

THE UNDERSIGNED, being the sole incorporator hereinbefore named, for the purpose of forming a corporation pursuant to the General Corporation Law of the State of Delaware, do make this Certificate, hereby declaring and certifying that this is our act and deed and the facts herein stated are true, and accordingly have hereunto set our hands this 21st day of July, 1999.

Erin L. Reilly, Incorporator